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Faculdade de Farmácia

RISK MANAGEMENT SYSTEMS - EXAMPLES OF PRACTICAL IMPLEMENTATION

Patrícia de Lurdes Douteiro Rodrigues

Dissertação orientada pelo Professor Doutor Helder Mota Filipe e coorientada pela Doutora Margarida Viana de Ferraz Guimarães

Mestrado em Regulação e Avaliação do Medicamento e Produtos de Saúde

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I dedicate this thesis to Francisco, my soul mate, for all the love, encouragement, dedication and patience with me.

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Abstract

Purpose

To demonstrate the impact of the new legislation of pharmacovigilance in the real-world context by the presentation of practical examples.

Methods

Critical analysis of the current pharmacovigilance legislation, as well as guidelines and recommendations from the European Medicines Agency (EMA).

Results

It will be presented a fictitious company risk management system, with its description of the risk management system through the Pharmacovigilance System Master File presentation and a concrete example of a Risk Management Plan of the medicinal product Isotretinoin with detailed implementation proposals of risk minimization measures, in line with the recommendations of the Pharmacovigilance Risk Assessment Committee (PRAC) for the recent referral procedure of retinoids.

Discussion/Conclusions

The new European Legislation in Pharmacovigilance and, consequently, the new regulatory requirements have increased the workload and complexity of pharmacovigilance. The focus of the pharmacovigilance system became a proactive, risk proportionate and patient-centered approach, with high level of transparency and engagement of civil society. This approach brings to fulfil previously unmet medical needs and reducing the burden of adverse drugs reactions by promoting the safeguard public health.

Keywords: Pharmacovigilance; Legislation; Pharmacovigilance System Master File; Risk management plan; Risk minimization measures, PRAC, Referral Procedure; Isotretinoin.

Resumo

Objetivo

Demonstrar o impacto da nova legislação de farmacovigilância no contexto do mundo real através da apresentação de exemplos práticos.

Métodos

Análise crítica da atual legislação de farmacovigilância, bem como *guidelines* e recomendações da Agência Europeia de Medicamentos (EMA).

Resultados

Irá ser apresentado um sistema de gestão de risco de uma empresa fictícia, com a sua descrição do sistema de gestão de riscos através da apresentação do dossier do Sistema de Farmacovigilância e de um exemplo concreto de um Plano de Gestão de Risco do medicamento Isotretinoína, com propostas detalhadas de implementação de medidas de minimização de riscos,.em consonância com as recomendações do Comité de Avaliação do Risco de Farmacovigilância (PRAC) em virtude do procedimento de arbitragem a acontecer com os retinóindes.

Discussão/Conclusões

A nova Legislação Europeia em Farmacovigilância e, consequentemente, os novos requisitos regulamentares aumentaram a carga de trabalho e a complexidade da farmacovigilância. O foco do sistema de farmacovigilância tornou-se uma abordagem pró-ativa, proporcional ao risco e centrada no paciente, com alto nível de transparência e envolvimento da sociedade civil. Esta abordagem permite satisfazer as necessidades médicas anteriormente não conhecidas e reduzir a carga de reações adversas a medicamentos, promovendo assim a salvaguarda da saúde pública.

Keywords: Farmacovigilância, Legislação, Dossiê Principal de Farmacovigilância; Plano de Gestão de Risco, Medidas de Minimização do Risco, PRAC, Procedimento de Arbitragem, Isotretinoína.

Abbreviations

ADR – Adverse drug reaction

AE(s) – Adverse Event(s)

aRMMs – Additional Risk Minimisation Measures

CAPA plan – Corrective and preventive action plan

CA – Competent Authority

DSUR – Development safety update report

EC – European Commission

EMA – European Medicines Agency

EU – European Union

EV– EudraVigilance

EVMPD – EudraVigilance Medicinal Products Dictionary

GVP – Good Pharmacovigilance Practices

ICSR(s) – Individual Case Safety Report(s)

MA – Marketing Authorization

MAA – Marketing Authorization Application

MAH – Marketing Authorization Holder

MedDRA – Medical Dictionary for Drug Regulatory Affairs

QA – Quality Assurance

QC – Quality Control

QMS – Quality management system

QPPV – Qualified person for Pharmacovigilance

QRD – Quality Review of Documents

PASS – Post-authorization Safety Study

PhV – Pharmacovigilance

PBRER – periodic benefit-risk evaluation reports

PIL – Package insert leaflet

PMS – Post-Marketing Surveillance

PRAC – Pharmacovigilance Risk Assessment Committee

PSMF – Pharmacovigilance system master file

PSUR – Periodic safety update report

PSUSA – Periodic Safety Update Single Assessment

RMM(s) – Risk Minimization Measure(s)

RMP(s) – Risk Management Plan(s)

RMS – Risk Management system

RMR – Reaction Monitoring Report

SmPAR – Summary Pharmacovigilance Assessment Report

SmPC – Summary of Product Characteristics

SOP – Standard Operating Procedure

XEVMPD – eXtended EudraVigilance Medicinal Product Dictionary

Table content

Content

1. Introduction

Pharmacovigilance is the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other medicine-related problem. The European Medicines Agency (EMA) coordinates the European Union (EU) pharmacovigilance system and operates services and processes to support pharmacovigilance in the EU [2].

Before a medicine is authorised for use, evidence of its safety and efficacy is limited to the results of clinical trials, where patients are selected carefully and followed up very closely under controlled conditions. This means that at the time of a medicine's authorisation it has been tested in a relatively small number of selected patients for a limited length of time [2].

In the post-marketing period, the product can be subject of use in settings largely different from the clinical trials before approval. In other words, a much larger population with a different range of co-morbidities or polymedicated may be exposed in a relatively short timeframe [2].

The safety information about the product is likely to change over time through its expanded use, specifically in terms of patient pool variations and the number of exposed population. Thus, market vigilance systems must be implemented and maintained after a drug has been launched in the market to detect safety issues that were not evident prior to commercialization [3].

Furthermore, the pharmacovigilance systems to be effective require the participation and cooperation of the patients, healthcare professionals, the pharmaceutical industry as well as the regulators, on the way that critical safety information can be identified and rapidly acted. In some instances, this has resulted in the withdrawal or restriction of drugs due to safety concerns that only emerged post-marketing [1,2].

1.1. Pharmacovigilance

According to the definition of World Health Organization (WHO), pharmacovigilance is the science that comprises activities relating to the detection, assessment, understanding and prevention of adverse effects or any other possible drug related problem [3].

The aforementioned definition comprehends the knowledge and all activities required for the safe and effective use of the medicinal products.

The European Medicines Agency (EMA) coordinates the European Union (EU) pharmacovigilance system and operates services and processes to support pharmacovigilance in the EU [2].

The specific aims of pharmacovigilance are to improve patient care and safety in relation to the use of medicines and all medical and paramedical interventions, improve public health and safety in relation to the use of medicines, contribute to the assessment of benefit, harm, effectiveness and risk of medicines, encouraging their safe, rational and more effective (including cost-effective) use, and promote understanding, education and clinical training in pharmacovigilance and its effective communication to the public [4].

There are several tools available for the monitoring of safety of medicinal products such as spontaneous reporting of Adverse Drug Reactions (ADRs), qualitative and quantitative signal detection, Periodic Safety Update Reports (PSURs), Risk Management Plans (RMPs) and also Post-authorisation Safety Studies (PASS) [5,6].

Spontaneous reporting of Adverse Drug Reactions (ADRs)

The spontaneous reports of adverse drug reactions are an important source for pharmacovigilance data, on which signal detection activities can be performed.
Signal detection may use both qualitative and quantitative approaches, such as manual review of individual cases and data mining tools. These tools are associated with several challenges and controversies [5,6]. Quantitative signal detection methods are based on statistical analysis and become more reliable when based on more data [7,8,9,10].

Qualitative and quantitative signal detection

Qualitative signal detection methods based on the review of cases may be less impacted by lower numbers but is more time consuming and requires trained specialists able to identify a trigger case, and maybe challenging in distinguishing an ADR from the disease being treated [10].

Periodic Safety Update Reports (PSURs)

PSURs are pharmacovigilance documents intended to provide a periodic evaluation of the risk-benefit balance of a medicinal product for submission by companies at defined time points during the post-authorisation phase [2].

Risk Management Plans (RMPs)

The RMP is the main planning instrument aimed to facilitate a more proactive approach in filling knowledge gaps through early planning of pharmacovigilance activities and it should ensure a feasible and risk-proportionate pharmacovigilance planning. Developing a RMP is a challenging task in view of the limited knowledge of the benefit risk profile at the time of marketing authorization. Nevertheless, it is a legal requirement and all companies must fulfil this obligation [11].

Post-Authorisation Safety Studies (PASS)

PASS are a tool to collect additional pharmacovigilance data [2]. These studies may have different approaches and designs. In order to overcome the related challenges, to implement these tools the European Commission has enhanced the importance of pharmacovigilance by developing a new legislation which includes a wide range of measures [12].

1.2. The importance of monitoring the safe use of medicines

The goal of monitoring and collecting data on ADRs is the rationalization of pharmacotherapy in order to use the most effective medicine with the least ADR upon the establishment of the proper diagnosis [13].

ADRs may be observed both during preclinical and clinical trials. Information on ADRs collected during these phases of drug development cannot predict a possible adverse event that may take place only after the placing of the medicinal product on the market. Among the main reasons are the fact that animal studies are insufficient to predict the safety of medicines in humans, the fact that in clinical trials only a limited number of selected patients is included, the conditions of administration of the medicine are different from those in normal clinical practice, the duration of trials is limited, and that data on rare serious adverse events, toxic effects of chronic treatment, the use of a medicine in specific categories of patients (children, the elderly, pregnant women) or interactions with other medicines are often incomplete or not available [13].

The most important source of new information on the unknown effects of medicines before its registration represents the fourth phase of clinical testing or monitoring of medicines. It starts after the registration is obtained and indicates that the medicine is in widespread, general use. This phase lasts indefinitely. During this period both harmful and beneficial unknown aspects of the drug are revealed. After placing a medicine on the market, manufacturers are obliged to monitor its safety, although this does not necessarily imply the organization of prospective studies about its ADRs [13].

Monitoring the safety of medicines on the market is a valuable tool for detecting ADRs that are the result of counterfeiting or inadequate quality of a medicine [13].
An organized and permanent monitoring of the effects of medicines after obtaining marketing authorisation is necessary to recognize and prevent ADRs on time [13].

Decision of withdrawal of medicines from the market due to the unfavorable ratio of benefits and risks is based on data collected by spontaneous reporting of adverse reactions [13].

1.3. History/background of Pharmacovigilance

Before 1950, the importance of post-marketing surveillance for new medicines was not considered as a commitment that should integrate each physician, patients and lawmakers as nowadays [14].

In 1962, the disaster of phocomelia associated with thalidomide was an eye-opening situation for the world about the importance of drug surveillance in clinical practice. Thalidomide was commercialized in several countries under many trade names and indicated for several therapeutic conditions. Phocomelia associated with thalidomide awoke the interest of all medical community and the governments around the world. For instance, the United Kingdom started a spontaneous reporting called the “yellow card” scheme. Similar activities were started in other countries such as Canada, Norway, Sweden, and Denmark in order to strengthen the patients’ safety and public health [14].

In 1968 the World Health Organization established an international Pharmacovigilance program “Program on International Drug Monitoring” that has been executed since 1978 by the international center for Pharmacovigilance that centralizes data about adverse effects collected by national Pharmacovigilance centers [14].

In the early 1970s another drug safety disaster occurred. This was the multi-system disorder known as the oculo-mucoctaneous syndrome caused by practolol (Eraldin) – a cardioselective betablocker used to treat angina and hypertension. The fundamental problem in this instance was a failure of timely identification despite having an early warning system in place [14].

The overriding message from Practolol was that spontaneous ADR reporting alone is insufficient as a means of studying pos-marketing safety. Thus, in the late 1970s various schemes designed to closely monitor the introduction of new drugs were suggested, but most of them were not implemented [14].

The Belgian Centre for Pharmacovigilance for medicines for Human use (BCPH) started its activities in 1976 after being recognized by the WHO. Since then the BCPH has been centralizing all reports of adverse effects concerning authorized medicines [14].

In 2001 the European Medicines Agency (EMA) launched EudraVigilance, a web-based information system designed to manage information on safety reports. Since then, it has

extended the system to allow commercial and non-commercial sponsors to report suspected unexpected serious adverse reactions (SUSARs) occurring during clinical trials electronically [15].

In 2002, more than 65 countries had their own Pharmacovigilance centers.

The International Conference on Harmonization (ICH) is a more formal group than Council for International Organizations of Medical Sciences (CIOMS) with a wider remit for harmonization across the drug development process. The main purpose is to harmonize existing guidelines from EU, USA and Japan, related to development and registration of medicines.
In relation to Pharmacovigilance, the key ICH guidelines and dates at which they were implemented are [16]:

- E2A: Definitions and Standards for Expedited Reporting (1994)
- E2B: Data elements for Electronic transmission of Individual Case Safety Reports (1997)
- E2C: Periodic Safety Update Reports for Marketed Drugs (1996)
- E2D: Post-approval Safety Data Management (2003)
- E2E: Pharmacovigilance Planning (2005)

The new Pharmacovigilance legislation in 2010/2012 brought significant changes related to the existing Pharmacovigilance requirements. More post-authorization safety and efficacy studies, a new Pharmacovigilance Risk Assessment Committee (PRAC) - the committee at the European Medicines Agency that is responsible for assessing and monitoring safety issues for human medicines, at the European Medicines Agency (EMA) and a broader reporting of side-effects by patients are among the new measures [2,17,18].

1.4. Regulatory Framework

The new Pharmacovigilance legislation, in force since July 2012, has brought one of the most significant changes to the regulation of human medicines in the European Union (EU). There were significant implications not only for applicants and holders of EU marketing authorisations, but also for patients, healthcare professionals (HCPs) and regulators [2,17,18].

The development of the pharmacovigilance legislation was based on the observation the adverse drug reactions (ADRs), 'noxious and unintended' responses to a medicine, being linked to around 197,000 deaths per year in the EU [2,17,18].

For this reason, in 2005, the European Commission began to review the safety monitoring European system. This included the sponsorship of an independent study, as well as a thorough public consultation throughout 2006 and 2007.
As a result of the these measures, in December 2010 a new Directive and Regulation was adopted by the European Parliament and Council of Ministers. This led to significant changes in the safety monitoring of medicines throughout the EU [2,17,18]:

- Directive 2010/84/EU
- Regulation (EU) No 1235/2010

This new legislation amended the existing pharmacovigilance laws contained in Directive 2001/83/EC and Regulation (EC) No. 726/2004. It was also accompanied by the Implementing Regulation, a legally binding act published by the European Commission in June 2012 that provides details on the operational aspects for the new legislation: Commission Implementing Regulation No 520/2012 of 19 June 2012 [2,17,18].

Additionally, practical measures to reinforce the new legislation are available for consultation in the guideline on Good Pharmacovigilance Practices (GVP). This guideline is applicable for MAHs, EMA and medicines regulatory in EU Members States (for all medicinal products: NAPs and CAPs) [2,17,18].

The GVPs describe practical measures to facilitate the performance of the pharmacovigilance practices in the EU. This guideline is divided into chapters which fall into two categories: modules covering major pharmacovigilance processes, and product or population-specific considerations. GVPs Modules from I to XVI cover major

pharmacovigilance processes and are available on the EMA website [1]. In fact, the GVP modules replaced Volume 9A of The Rules Governing Medicinal Products in the European Union – Guidelines on Pharmacovigilance for Medicinal Products for Human Use [12].

EU law therefore requires each MAH, national competent authority and EMA to operate a pharmacovigilance system. The overall EU pharmacovigilance system operates through cooperation between the EU Member States, EMA and the European Commission. In some Member States, regional centers are in place under the coordination of the national competent authority [2].

1.5. Aims of the pharmacovigilance legislation

The overall main purpose of the new pharmacovigilance legislation is to reduce the number of ADRs in the EU through [3,17]:

- the collection of quality data of medicines and their safety;
- rapid and robust assessment of issues related to the safety of medicines;
- effective regulatory action required to deliver safe and effective use of medicines;
- empowerment of patients through the increase in reporting and participation;
- increased levels of transparency and better communication.

The legislation made therefore an impact on marketing-authorisation holders and applicants. It aimed to make their roles and responsibilities clearer, minimize duplication of effort, release resources by rationalizing and simplifying reporting on safety issues, and establish a clear legal framework for post-authorisation monitoring [3,17].

1.6. Pharmacovigilance Risk Assessment Committee

The Pharmacovigilance Risk Assessment Committee (PRAC) is the European Medicines Agency's (EMA) committee that is responsible for assessing all aspects of the risk management of medicines for human use across the European Economic Area, from signal management to periodic safety update reports (PSURs) and risk management plans (RMPs). It is also involved in the design and evaluation of some post-authorisation safety studies (PASS) and coordinates the European PV agency inspection programme [19,20].

The main responsibility of PRAC is to prepare recommendations on any questions relating to PhV activities of a medicine for human use, on signal management, and on risk-management systems, including monitoring of the effectiveness of such systems [19,20].

Where necessary, the PRAC can impose a PASS to the Marketing Authorisation Holder of a medicinal product as a condition of the marketing authorisation or a specific obligation under exceptional circumstances. PASS may be also be required by the PRAC to investigate a safety concern in the product risk management plan or to evaluate the effectiveness of risk minimisation activities [19,20].

A particular focus in 2017 was signal management, with the introduction of enhanced Eudravigilance functionality on 22nd November 2017 and associated requirements for the industry to forward all validated signals to PRAC for evaluation [19].

A recently published document by EMA, on April 21, 2017, states that since its establishment in September 2012, PRAC has discussed and make the results public of its discussions on more than 600 signals [19].

The PRAC make available recommendations on issues on pharmacovigilance and risk management systems, including the monitoring of their effectiveness, to the [20]:

- Committee for Medicinal Products for Human Use (CHMP) for centrally authorized medicines and referral procedures;
- Coordination Group for Mutual Recognition and Decentralised procedures – Human (CMDh) on the use of a medicine in Member states;
- the EMA secretariat, Management Board and European Commission, as applicable.

Important safety Issues via Referrals

A referral is a procedure used to resolve issues such as concerns over the safety or benefit-risk balance of a medicine or a class of medicines [34].

In a referral, the European Medicines Agency is requested to conduct a scientific assessment of a specific medicine or class of medicines on behalf of the European Union (EU). The medicine, or the class of medicines, is 'referred' to the Agency so that it can make a recommendation for a harmonized position across the EU [34].

Relevant information from the literature, including pharmacoepidemiological studies and meta-analysis, from non-clinical studies, spontaneous reports and clinical trials, and any available academic research are fed into the assessment. Referrals offer opportunities for involving scientific advisory groups and for engaging patients and researchers, who can each contribute to the assessment from their specific angle. A referral can be triggered for products belonging to any therapeutic class, including both established and innovative medicines. Results of referral procedures contribute towards an optimised use of medicinal products. For instance, they have recently led to new recommendations to minimise the risk of teratogenicity in patients taking isotretinoin. Information on the commencement of the referral, the timetable, list of affected products and questions for the MAHs is promptly published on the EMA's website [36], thus allowing real-time transparency. Relevant MAHs are notified and asked to contribute to the referral, including the provision of data and information for the PRAC's assessment. The PRAC recommendation on the safety issue is then forwarded to the Committee for Medicinal Products for Human Use for opinion or, if no CAPs is involved, to the Coordination Group for Mutual Recognition and Decentralised Procedures—Human for its agreement. Once the evaluation is concluded, the PRAC assessment report outlining the outcome of the referral procedure is also published on the EMA website. Safety referrals are a very effective pharmacovigilance instrument to coordinate a thorough and timely review of the safety of products including those authorised via different procedures. Referrals result in a harmonised position across the EU, ratified by a decision that is immediately implementable and legally binding for all the MSs [22].

1.7. Quality management system

To fulfill the requirements of the legislation, MAHs, NCAs and the EMA have to establish and use adequate and effective quality systems. A quality system comprehends the settling of structures and processes (quality planning), the carrying out of tasks and responsibilities in accordance with quality requirements (quality adherence), the monitoring and evaluation of effectiveness of structures and processes (quality control and assurance) and the correction and improvement when necessary (quality improvements). The overall quality objectives of a pharmacovigilance system are to comply with the task and responsibilities set up in the legislation, prevent ADRs and promote the safe and effective use of medicinal products, thus contributing to public health [22,23].

For every authorized medicinal product, MAHs are required to maintain a description of their pharmacovigilance system in the pharmacovigilance system master file, which includes information relating to the persons (e.g. qualified person responsible for pharmacovigilance in the EU), as well as of the procedures put in place to ensure the safety of medicines. A copy of the pharmacovigilance system master file may be requested at any time and is usually requested during pharmacovigilance inspections. The EMA and the MSs need to cooperate and maximise their resources to continuously develop pharmacovigilance systems capable of achieving high standards of public health protection for all medicinal products, regardless of the routes of marketing authorisation. Additionally, to facilitate interaction between NCAs, the EMA, the EC and MAHs, competent authorities have to keep accessible descriptions of their organisational structures, assignment of tasks and responsibilities, and contact points [22,23].

1.8. Pharmacovigilance System Master File

1.8.1. Definition

The Pharmacovigilance system master file (PSMF) definition is provided in Article 1(28e) of Directive 2001/83/EC as “a detailed description of the pharmacovigilance system used by the marketing authorisation holder with respect to one or more authorized medicinal products”. The minimum requirements for its content and maintenance are detailed in the Commission Implementing Regulation (EU) No 520/2012.

The detailed requirements provided by the Commission Implementing Regulation are further supported by the guidance in GVP Module II of the Good Vigilance Practice(s) [21].

In summary, the PSMF comprehends all aspects of pharmacovigilance activities, including information on the tasks that are subcontracted. The marketing authorization holder retains ultimate responsibility for compliance with the legal arrangements [21].

Additionally, the PSMF is used as a basis to the appropriate arrangement and conducting of the marketing authorization holder’s audits as well as a tool for EU Qualified Person for Pharmacovigilance (QPPV) to maintain supervision over the PhV System. The PSMF must be permanently available for inspection by the relevant competent authorities to verify its compliance with all aspects of the pharmacovigilance system [21].

1.8.2. Location

The location of the PSMF should be either at the site in the EU where the major pharmacovigilance activities of the MAH are performed, or at the place in the EU where the qualified person responsible for pharmacovigilance operates. Its location or any changes are required to be entered and immediately updated both in the extended Eudravigilance Medicinal Product Dictionary (XEVMPD) and on the European medicines web portal [21].

The PSMF possesses a unique code, the reference number, which is assigned by the Eudravigilance (EV) system, when the location information of PSMF with the format of Extended Eudravigilance Medicinal Product Report Message (XEVPRM) is entered [21].

When submitting a Marketing Authorisation request, the applicant shall include the location of the PSMF electronically and its reference number in the application [21].

The PSMF may be stored either in paper or in electronic form. It can be a digital document, existing either on different servers of the company or at suppliers of data services, but a clearly arranged printed copy must be directly available for inspection at the office address [21].

1.8.3. Contents of the Pharmacovigilance System Master File

Except for aspects covered by the article 8 of Directive 2001/83/EC related to changes to the summary of the pharmacovigilance system, including, for instance, changes to the location of PSMF or the QPPV's name and his or her contact details, other changes of the content of PSMF do not have to be notified to the Competent Authority and are not expected to require a variation request [21].
In former cases, those changes should be immediately notified to the Agency as well as being accompanied by an update of the Eudravigilance database, and where necessary, an update of the European medicines web-portal [21].
It should be included in the summary of the applicant's pharmacovigilance system [21]:

- Proof that the applicant has at his disposal a qualified person responsible for pharmacovigilance (QPPV);
- The Member States in which the qualified person has their residence and carries out his/her tasks;
- The contact details of the qualified person;
- A statement signed by the applicant referring that the applicant has the necessary means to fulfil the tasks and responsibilities listed in Title IX;
- Reference to the location where the pharmacovigilance system master file is kept.
- The minimum requirement for contents of the PSMF and its maintenance are set out in the Commission Implementing Regulation (IR) (EU) No 520/2012 on the performance of pharmacovigilance activities for in Regulation (EC) No 726/2004 and Directive 2001/83/EC.
- The following elements should be included in the PSMF:
- Information referring to the Qualified Person for Pharmacovigilance (QPPV): with the description of his responsibilities where he has enough authority over the pharmacovigilance system to promote, maintain and improve compliance with

predestined tasks and responsibilities; contact details; Curriculum Vitae; proof of his registration in Eudravigilance database; a description of an alternative to be followed in the absence of the QPPV; and a contact person for the pharmacovigilance where such person is introduced at the national level in accordance with the Article 104(4) of Directive 2001/83/EC, including contact details;

- The organizational structure of the MAH, which shall include the sites where different pharmacovigilance activities take place (individual case safety report collection, evaluation, safety database case entry, periodic safety update report production, signal detection and analysis, risk management plan management, pre- and post-authorization study management and management of safety variations to the terms of a MA);
- The description of the computerized systems and databases used to handle the safety information, including an assessment of their capabilities and their fit for this purpose;
- Description of how data is handled, recorded and the processes used for each of the pharmacovigilance activities: risk-benefit monitoring, operation of the RMP and monitoring of the results of RMM. Collection, evaluation and reporting of individual case safety reports, preparation and submission of periodic safety update report, procedures for communicating the safety concerns with healthcare professionals as well as general public, and implementation of safety variations to the summary of product characteristics and package leaflet;
- The content of the quality system, including the location of qualification records of the personnel, a summary of the training concept with reference to the training files, instructions and critical processes. It must include the presentation of the record management system with reference to the site where the documents used in PhV activities are, and the description of the how the performance of the PhV System is monitored;
- Lastly, a description of the activities and/or services subcontracted by the MAH, when applicable.

1.8.4. Contents of Annex of the Pharmacovigilance System Master File

As for the Annexes of the PSMF it should include:

1. Annex A: The Curriculum Vitae of the QPPV and associated documents, lists of the QPPV's delegated activities and the persons, as well as to whom they are delegated;

2. Annex B: A list of contracts and agreements, including the subcontractors;

3. Annex C: Lists of the safety data sources, including affiliates and third party contacts;

4. Annex D: A list of computerized systems and databases;

5. Annex E: Lists of written policies and procedures, for the specific quality system and processes to ensure:

a. the continuous monitoring of pharmacovigilance data and risk minimization activities of the MAH;

b. scientific evaluation of the risks of medicinal products by the MAH;

6. Annex F: Lists of performance indicators used by the MAH and the results of performance assessment to continuously assure the good performance of pharmacovigilance activities;

7. Annex G: scheduled and completed audits;

8. Annex H: A list of all medicinal products covered by the PSMF and the name of Member State(s), in which the medicinal product is authorized (this list should be organized in accordance with the Active Substances and shall refer to the type of procedure for authorization and procedure number and presence of medicinal product on the market in the EU and other (non-EU) territories);

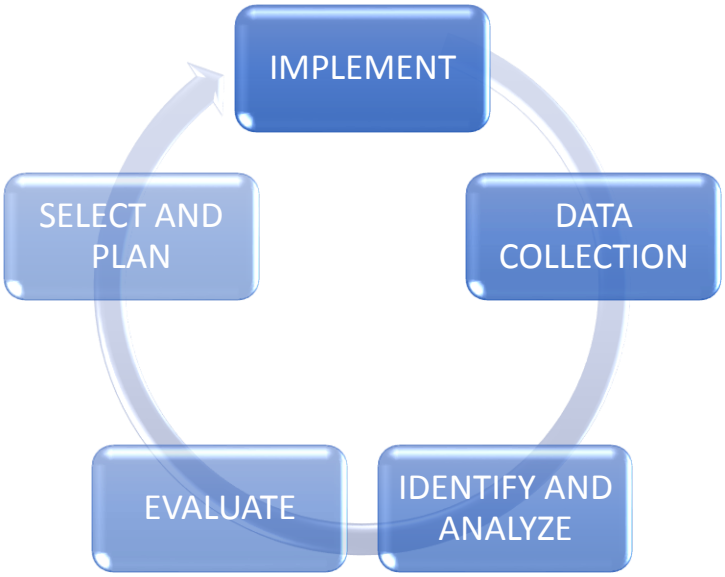
9. Annex I: A logbook, which ensures that any changes in the contents of PSMF, made within the previous 5 years, will be recorded referring to the person responsible for the alteration and the reason for that change (where appropriate).

1.9. Risk Management System

1.9.1. Definition

A Risk Management System (RMS) can be defined as a set of Pharmacovigilance activities and interventions designed to identify, characterize, prevent or minimize risks relating to medicinal products including the assessment of the effectiveness of those activities and interventions [9].

Figure 1: Risk Management cycle



A RMP is a detailed description of the RMS for a medicinal product and its requirement was firstly introduced in the EU legislation (the Regulation) in 2005.

A RMP summarizes the safety profile of a medicinal product, registers the safety concerns such as the important identified risks, important potential risks as well as the missing information, and lists the further studies that will be carried out after the marketing authorization as well as any applicable Risk minimization measures [24].

For MAs granted after 21 July 2012, MAHs must operate a RMS for each medicinal product. Holders of MAs granted before this time are not required to operate a RMS for those medicinal products unless either the regulator or the MAH are concerned about risks affecting the benefit–risk profile of previously authorized medicinal product [24].

When a RMS for a medicinal product is created, it is mandatory that the MAH:

- Ensures that the risks of their medicines are constantly being monitored in accordance to the legislation, as well as to report the results to the appropriate Competent Authority if applicable;
- Takes all necessary measures to minimize the risks of their products and maximizes the benefits, including ensuring that the information is accurately produced by the company, and actively updating and communicating it when new information becomes available [24].

1.9.2. Risk Management Plan (RMP)

The Risk Management Plan is a detailed description of the risk management system, and may contain the Safety Specifications, the Pharmacovigilance Plan, and the Risk Minimization Plan. The RMP is a dynamic document that should be updated throughout the life cycle of the medicinal product [24].

Guidance on format of the RMP in the European Union may be found in the related EMA guidance [27], and the content of the document is compiled according to the Guideline on good Pharmacovigilance Practices (GVP) Module V [26].

The RMP is a detailed description of the risk management system, and should contain three main sections (it will be described, further ahead, in more detail):
- Safety Specification
- Pharmacovigilance Plan
- Risk Minimisation Plan

The purpose of the Safety Specifications is to explicitly consider the level of safety that has been demonstrated so far. It should identify what is already known about safety and what is not yet known. The Safety Specifications are a set of important identified risks, important potential risks as well as missing information. These are not meant to describe all the identified ADRs for the product but to identify the important risks of the product as well the missing information (e.g. special populations) which might have a significant impact on the B/R balance of the product and are passive and in need of further characterization [24,26].

The Pharmacovigilance Plan should indicate how this further characterization will be achieved in practice. It should contain the:
- Expected levels of use of the product over time;
- Strategies to address existing and potential safety signals;

- Strategies to monitor recognized serious ADRs in order to ensure that their incidence is low;
- Strategies to address areas where safety knowledge is incomplete;
- Proposed milestones at which a greater level of safety experience is expected to have demonstrated.

Sometimes the Pharmacovigilance plan alone may not provide sufficient safeguards against known or serious potential hazards. In these cases, a Risk Minimization Plan is required.

A risk minimization plan includes a set of Risk Minimization Measures (RMMs) which are a set of activities that need to be implemented in order to prevent or at least reduce the risk of harm from the event associated with a particular safety concern [29].

Following the review of the RMP, the summary for the public is shared with the company prior to publication and published at the time as part of the European Public Assessment Report (EPAR) (at time of Commission decision; this activity started in 2014 at the level of the EMA for CAPs). Important to note is that this is linked to the product information, European Public Assessment Report summary and list of medicines under additional monitoring. It shall not be forgotten that the RMP shall be continuously updated during the lifecycle of the medicinal products and updates should be submitted when major variations occur such as new indications, restrictions of indication, new or updated contraindications, new important risks or important changes to known risks, and any 'additional risk minimization measures' are added or removed. This is within the concept of the continuous circle of collecting data, reporting and evaluating the B/R profile and confirming whether it remains favorable [24,26].

1.9.3. Objectives of RMP

The RMP must contain the following elements which:

- Identify or characterize the safety profile of the medicinal product(s) including what is known and not known and, importantly, which risks need to be characterized or managed proactively (the "safe specification");

- Plan pharmacovigilance activities to characterize and quantify serious or clinically relevant risks of adverse reactions and to identify new adverse reactions (the "Pharmacovigilance Plan");

- Plan and implement risk minimization measures, including the evaluation of the effectiveness of these activities (the “Risk Minimization Plan).

1.9.4. Content of the RMP

The RMP is divided into several sections, organized into modules to increase flexibility [26]:

- Part I Product(s) Overview
- Part II Safety Specification
  - Module SI: Epidemiology of the indication(s) and target population(s)
  - Module SII: Non-clinical part of the Safety Specification
  - Module SIII: Clinical trial exposure
  - Module SIV: Populations not studied in clinical trials
  - Module SV: Post-Authorization Experience
  - Module SVII: Identified and potential risks
  - Module SVI: Additional EU requirements for the Safety Specification
  - Module SVIII: Summary of the safety concerns
- Part III Pharmacovigilance Plan- Routine Pharmacovigilance activities
- Part IV Plans for post-authorization efficacy studies
- Part V Risk minimization measures (including evaluation of the effectiveness of risk minimization measures)
- Part VI Summary of the RMP
- Part VII Annexes

1.9.5. Updated and Timelines to the RMPs

At the time of application for a marketing authorization companies submit a risk management plan (RMP), although in some circumstances certain parts can be omitted (for instance in generics) [26].

As new data is available, RMPs are continually modified and updated throughout the lifecycle of the medicine. Companies need to submit an updated RMP:
- at the request of NCA or by the Agency;
- every time the risk management system is changed, in particular because of new information that is raised which may lead to a significant change of the benefit/risk balance, or as a result of an important pharmacovigilance or risk-minimisation milestone being met. In case an RMP is previously submitted by the applicant, the following

submissions must be in the form of an update, unless requested otherwise. Each submission of the RMP will have an indicative version number and date [26].

1.9.6. Risk Minimization Measures (RMMs)

The objective of the Risk minimisation measures is to prevent or reduce the appearance of adverse reactions, or to reduce their severity and impact on life quality of the patient. It is vital that these RMMs be planned and implemented, and its effectiveness be evaluated [29].

Routine measures are applied to every medicinal product. In addition, further risk minimisation activities should only be addressed when they are deemed to be essential for the safe and effective use of the drug [29].

Therefore, RMMs typically are classified in two types [29]:

- Routine risk minimization: comprehending product information updates, such as changes of the legal status, packing size, SmPC, Package leaflet and Labelling;
- or Additional Risk Minimization: consisting in the control or restriction of the product's access or use, distribution of educational materials or providing training programs (e.g. prescription checklists, pregnancy prevention programs, patient alert cards, others), as well as the distribution of Direct Healthcare Professionals Communications (DHPC).

The Directive 2001/83/EC indicates that MAH should "Monitor the outcome of risk minimisation measures which are described in the RMP or which are laid down as conditions of the MA". The Directive and the Regulation (EC) No 726/2004 also include provisions for the agency and NCA to monitor the outcome of the RMM.

Beyond studies and measures described in the risk management plan, the PRAC assess both protocol and results of imposed post-authorisation safety studies aiming the evaluation of the effectiveness of risk minimization measures [29].

1.10. Periodic safety updated report (PSUR)

The PSUR presents a comprehensive and critical analysis of the B/R balance of the medicine, submitted by the MAHs at defined time points throughout the post-authorisation phase. It considers new and emerging data in the context of cumulative information about risks and benefits [30].

The objective of the Periodic Safety Update Reports (PSURs) is to facilitate the regular and systematic review of the global safety data available to MAH. The goal of such review of the data in the PSUR may lead to new safety issues being identified [30].

The development of PSURs starts when a drug is first approved for marketing anywhere in the world and, initially, reports are produced on a six-monthly basis. The period covered becomes longer once the drug is established in the market [30].

PSUR reporting should be linked to the risk management plans (RMPs) of a medicinal product. The “modular approach” of the PSUR described in GVP Module VII intends not only to minimise the duplication but also to improve efficiency during the preparation and review of PSURs along with other regulatory documents such as the development safety update report (DSUR) or the safety specification in the RMP [30].

1.10.1. Format and content of PSUR

The new format is described in *GVP Module VII.* The *GVP Module VII* provides guidance on the preparation, submission and assessment of PSURs. The format and content of PSURs in the EU are based on those for the Periodic Benefit Risk Evaluation Report (PBRER) described in the *ICH-E2C.*

The PSUR should be based on all available data and shall focus on new information which has been obtained since the data lock point of the last PSUR. It should be taken into account cumulative information when performing the overall safety evaluation and integrated benefit-risk assessment [30].

The PSUR should present summaries of data that are relevant to the benefits and risks of the product, including results of all studies with a consideration of their potential impact on the marketing authorisation [30].

1.10.2. Timelines and submission of PSUR

Marketing authorisation holders for products authorised before 2nd July 2012, for centrally authorised products, and 21st July 2012, for nationally authorised products, and for which the frequency and dates of submission of PSURs are (a) not a condition to the marketing authorisation or (b) determined otherwise in the list of Union reference dates (EURD List) shall submit PSURs according to the submission schedule below:

- At 6 months intervals once the product is authorised, even if it is not marketed;
- Once a product is marketed, a 6 monthly PSUR submission should be continued following initial placing on the market in the EU for 2 years, and afterwards once a year for the following 2 years, and thereafter at 3-yearly intervals.

1.10.3. List of European Union Reference dates

The list of Union reference dates, and frequency of submission of periodic safety update reports, is a list of active substances and its combinations for which Periodic Safety Update Reports should be submitted in accordance with the EU reference dates and frequencies determined by the Committee for Medicinal Products for Human Use (CHMP) and the Coordination Group for Mutual Recognition and Decentralized Procedures - Human (CMDh), following consultation with the Pharmacovigilance and Risk Assessment Committee (PRAC) [32].

The EU reference dates list has been compiled to facilitate the harmonization of Data Lock Points (DLPs) and frequency of submission of PSURs for medicinal products containing the same active substance, or a combination of these, subject to different marketing authorisations authorised in more than one Member State [32,32].

1.10.4. PSUR vs RMP

While PSUR is retrospective, with an integrated approach, and the assessment of the risk-benefit is performed during the post- authorisation period, the RMP is prospective and its risk-benefit management and planning are done either during the pre- and post-authorisation period. Thus, the two files are complementary [25,30].

During the preparation of a PSUR, the marketing authorisation holder should consider if any identified or potential risk discussed in the PSUR is important and requires an update of the RMP [25,30].

If so, an updated and revised RMP including the new important safety concern should be submitted with the PSUR and assessed in parallel, following the timetable for the assessment of PSUR as described above [30].

If the important safety concern is identified by the national competent authority during the assessment of a PSUR and no updated RMP or no RMP had been submitted, the agency will typically recommend submitting an updated or a new RMP within a defined timeline [30].

2. Methods

The main purpose of this work is to demonstrate the complexity of the pharmacovigilance system and its regulatory requirements by presenting practical examples in the real world. The methods used for the performance of this practical work was the public revision of the Current European Legislation, Guidelines and recommendations found in the EMA Website and European Commission.

Main ideas:

- Pharmacovigilance is a dynamic and complex area. Understand how the processes work in practice is the focus of this work.
- Creation of a fictional company and attempt to implement the main PhV requirements, namely the PSMF and the RMP.
- The medicinal product chosen for this discussion was isotretinoin mainly due to:
    - The well know adverse reactions (mainly teratogenicity).
    - Ongoing safety referral procedure triggered by the negative outcome of the evaluation of the effectiveness of the existing RMM in place (e.g. PPP).
    - Understand all measures which need to be applied by the MAH following the PRAC recommendations in order to increase the safety of isotretinoin and ultimately optimise the use of the product.

3. Results

In the following pages it will be demonstrated practical examples of a Pharmacovigilance System Master File presentation, in the fictional company Stala Pharma, as well as the importance of the Risk Management Plan through a practical example of the medicinal product Isotretinoin Generic with detailed proposals of implementation of risk minimization measures.

Pharmacovigilance System Master File of Stala Pharma

Content

Abbreviations

ADR – Adverse drug reaction

AE(s) - Adverse Event(s)

CAPA plan - Corrective and preventive action plan

CAs – Competent Authorities

CV – *Curriculum Vitae*

DSUR – Development safety update report

EV - EudraVigilance

EVMPD - EudraVigilance Medicinal Products Dictionary

GVP – Good Pharmacovigilance Practices

ICSR(s) - Individual Case Safety Report(s)

MA - Marketing Authorization

MAA - Marketing Authorization Application

MAH – Marketing Authorization Holder

MedDRA-Medical Dictionary for Drug Regulatory Affairs

QA – Quality Assurance

QC – Quality Control

QMS- Quality management system

QPPV – Qualified person for Pharmacovigilance

QRD - Quality Review of Documents

PASS- Post-authorization Safety Study

PhV- Pharmacovigilance

PBRER- periodic benefit-risk evaluation reports

PIL- Package insert leaflet

PMS - Post-Marketing Surveillance

PRAC - Pharmacovigilance Risk Assessment Committee

PSMF – Pharmacovigilance system master file

PSUR – Periodic safety update report

PSUSA - Periodic Safety Update Single Assessment

RMM(s) - Risk Minimization Measure(s)

RMP(s) - Risk Management Plan(s)

RMR - Reaction Monitoring Report

SmPAR - Summary Pharmacovigilance Assessment Report

SmPC – Summary of Product Characteristics

SOP - Standard Operating Procedure

XEVMPD - eXtended EudraVigilance Medicinal Product Dictionary

***Table 1*-Traceability Report**

ID	Section	Description	Traceability	Revised by	Approved by	Last modified on	Validity
IIB4 rev00	Cover Page		Original document	Joana Silva	Patrícia Rodrigues	27-11-2016	2 years 27-11-2018
IIB41 rev00	Qualified person responsible for pharmacovigilance (QPPV)		Original document	Joana Silva	Patrícia Rodrigues	27-11-2016	2 years 27-11-2018
IIB42 rev00	The organisational structure		Original document	Joana Silva	Patrícia Rodrigues	27-11-2016	2 years 27-11-2018
IIB43 rev00	The sources of safety data		Original document	Joana Silva	Patrícia Rodrigues	27-11-2016	2 years 27-11-2018
IIB44 rev00	Computerised Systems and Databases		Original document	Joana Silva	Patrícia Rodrigues	27-11-2016	2 years 27-11-2018
IIB45 rev00	Pharmacovigilance Process		Original document	Joana Silva	Patrícia Rodrigues	27-11-2016	2 years 27-11-2018

ID	Section	Description	Traceability	Revised by	Approved by	Last modified on	Validity
IIB46 rev00	Pharmacovigilance system performance		Original document	Joana Silva	Patrícia Rodrigues	27-11-2016	2 years 27-11-2018
IIB47 rev00	Quality system		Original document	Joana Silva	Patrícia Rodrigues	27-11-2016	2 years 27-11-2018
IIB48.1 rev00	Annex A		Original document	Joana Silva	Patrícia Rodrigues	27-11-2016	2 years 27-11-2018
IIB48.2. rev01	Annex B	List of contracts and agreements	Revised document	Joana Silva	Patrícia Rodrigues	30-11-2016	2 years 30-11-2018
IIB48.3 rev01	Annex C	- List of affiliates and third party contacts - List of studies and programs	Revised document	Joana Silva	Patrícia Rodrigues	04-12-2016	2 years 04-12-2018
IIB48.4 rev00	Annex D	List of computerized systems and Databases	Original document	Joana Silva	Patrícia Rodrigues	27-11-2016	2 years 27-11-2018

ID	Section	Description	Traceability	Revised by	Approved by	Last modified on	Validity
IIB48.5 rev00	Annex E	List of procedural documents	Original document	Joana Silva	Patrícia Rodrigues	27-11-2016	2 years 27-11-2018
IIB48.6 Rev00	Annex F	- List of performance indicators - Performance assessment in relation to the indicators	Original document	Joana Silva	Patrícia Rodrigues	27-11-2016	2 years 27-11-2018
IIB48.7 rev00	Annex G	- Audit schedules - List of audits conducted and completed	Original document	Joana Silva	Patrícia Rodrigues	27-11-2016	2 years 27-11-2018
IIB48.8 rev01	Annex H	List of products	Revised document	Joana Silva	Patrícia Rodrigues	7-12-2016	2 years 07-12-2018
IIB48.9 rev00	Annex I	- Logbook - History of changes according to the annex A-H	Original document	Joana Silva	Patrícia Rodrigues	27-11-2016	2 years 27-11-2018

Table 2 - Copy Control

Number of copies	Located at
1 copy	General manager
1 copy	Pharmacovigilance Department
1 copy	Dr. Helder Mota
1 copy	Dr. Margarida Guimarães
6 copies	University of Lisbon - Faculty of pharmacy

Table 3 - Content of the PSMF

Control	Section	Name
IIB4 rev00	-	Cover page
IIB41 rev00	1	Quality Person for Pharmacovigilance
IIB42 rev00	2	Organisation Structure
IIB43 rev00	3	The sources of Safety Data
IIB44 rev00	4	Computerised Systems and Databases
IIB45 rev00	5	Pharmacovigilance Process
IIB46 rev00	6	Pharmacovigilance System Performance
IIB47 rev00	7	Quality system
IIB48.1 rev00	A	List of delegated tasks CV of QPPV CV of Deputy QPPV Job description of QPPV Job Description of Deputy QPPV Proof of registration with EudraVigilance
IIB48.2 rev01	B	List of contracts and agreements
IIB48.3 rev01	C	List of affiliates and third-party contacts List of studies and programs
IIB48.4 rev00	D	Overview of computerised systems and Databases Overview of Databases
IIB48.5 rev00	E	List of procedural documents
IIB48.6 rev00	F	List of performance indicators Performance assessment in relation to the indicators
IIB48.7 rev00	G	Audit schedules List of audits conducted and completed
IIB48.8 rev01	H	List of products
IIB48.9 rev00	I	Logbook History of changes according to the annex A-H

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Cover Page

Pharmacovigilance System Master File

XEVMPD Code: MFL0030

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Marketing Authorisation Holder Contact Details:

Name: **Stala Pharma - Pharmaceutical Products, S.A. (Stala Pharma P)**

Address: Rua Alexandre Pinto, nº105, 3º esq, 2800-039

Lisbon – Portugal

Name: **Stala Pharma - Generics, S.A. (Stala Pharma G)**

Address: Rua Alexandre Pinto, nº105, 3º esq, 2800-039

Lisbon – Portugal

The Stala Pharma - Pharmaceutical Products, S.A. shares the same pharmacovigilance system master file with Stala Pharma - Generics, S.A.

Qualified Person for Pharmacovigilance Name address and contact details

Name: Patrícia de Lurdes Douteiro Rodrigues

Address: Rua Alexandre Pinto, nº105, 3º esq, 2800-039 Lisbon, Portugal

Telephone: +351211122333

Mobile (24-hour): +351911122333

E-mail address: PhV@stalapharma.pt

Section I

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II.B.4.1. Qualified person responsible for pharmacovigilance (QPPV)

As part of the pharmacovigilance system, the MAH shall have permanently and continuously at its disposal an appropriately qualified person responsible for pharmacovigilance in the EU (QPPV) [DIR Art 104(3)((1)a)]. Each pharmacovigilance system can have only one QPPV.

The MAH shall ensure that the QPPV has sufficient authority to influence the performance of their quality system as well as their pharmacovigilance activities. The MAH should therefore ensure that the QPPV has access to the PSMF as well as authority over it and is notified of any changes to it. The authority over the pharmacovigilance system and the PSMF should allow the QPPV to implement changes to the system and to provide input into RMPs.

Overall, the MAH should ensure that structures and processes are in place, so that the QPPV can fulfil their responsibilities and therefore, the MAH should ensure that mechanisms are in place so that the QPPV receives all relevant information and that the QPPV can access all information the QPPV considers relevant, in particular on:

• emerging safety concerns and any other information relating to the benefit-risk evaluation of the medicinal products covered by the pharmacovigilance system;

• ongoing or completed clinical trials and other studies the marketing authorisation holder is aware of and which may be relevant to the safety of the medicinal products;

• information from sources other than from the specific marketing authorisation holder, e.g. from those with whom the marketing authorisation holder has contractual arrangements;

•the procedures relevant to pharmacovigilance which the marketing authorisation holder has in place at every level in order to ensure consistency and compliance across the organisation.

Thus the QPPV should be have adequate theoretical and practical knowledge for the performance of pharmacovigilance activities [IR Art 10(1)]. The QPPV should have skills for the management of pharmacovigilance systems as well as expertise or access to expertise in relevant areas such as medicine, pharmaceutical sciences as well as epidemiology and biostatistics. The MAH should provide the QPPV with training in relation to its pharmacovigilance system, which is appropriate for the role prior to the QPPV taking up the position and which is appropriately documented. Consideration should be given to additional training, as needed, of the QPPV in the medicinal products covered by the pharmacovigilance system.

The designated EEA Qualified Person for Pharmacovigilance of the Stala Pharma is Patrícia Rodrigues and the Deputy-QPPV is Joana Silva.

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The authority of the EEA Qualified Person for Pharmacovigilance over the pharmacovigilance system is ensured via the Pharmacovigilance Group Policy, as well as by a SOP and the respective job description in annex A.

The responsibilities of the EEA Qualified Person for Pharmacovigilance can be summarized as follows:

- Have access to and ensure that the Pharmacovigilance System Master File (PSMF) is in place, is accurate and up to date;
- Maintain an overview of the safety profiles and of any emerging safety issues of the company products. Act as the local pharmacovigilance contact point for the regulatory authorities on a 24-hour basis and also as a contact point for pharmacovigilance audits or inspections;
- Maintain awareness of the any conditions or obligations adopted as part of the Marketing Authorization as well as any risk minimization measures;
- Have authority and sign off on Risk Management Plans (RMPs). The QPPV usually signs off on PSURs and DSURs also;
- Being involved in the revision and sign-off of protocols of PASS;
- Having consciousness of PASS requested by a competent authority including results of such study;
- Ensuring that Quality Control (QC) and Quality Assurance (QA) mechanisms are in place to keep the MAH in compliance;
- SOPs and Working Documents covering PV are in place, up-to-date, trained on and actually followed;
- A quality management system (QMS) is in place which includes audits, inspections, Corrective Action, Preventive Action plans (CAPAs) as needed and that they are actually put in place and completed;
- Ensuring a full and prompt response to any request by the competent authority or by the agency for prevision of additional information;
- Ensuring that PV training is done in the drug safety/PV department as well as anywhere (everywhere) else in the company (or vendors, third parties etc.) where safety matters may arise;
- Ensure that written agreements with other companies (including business partners, vendors, and other third parties) are in place regarding safety and oversee their work;
- Ensure that signal detection and trending mechanisms are in place;
- Ensure that all suspected adverse drug reactions ADRs received by the MAH are collected and accessible at one or more points in the EU;
- Ensure that ICSRs, PSURs and Post-Authorization Safety Studies (PASS) cases and any other safety commitments are reported appropriately to the competent authorities (CAs) and the Agency;
- Ensure the continued evaluation of the benefit/risk analyses of all products;

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- Ensure the conduct of pharmacovigilance and submission of all pharmacovigilance-related documents in accordance with the legal requirements and GVP;
- Provide input into the preparation of regulatory actions in response to emerging safety concerns (e.g. variations, urgent safety restrictions, and communication to patients and healthcare professionals).

1. Summary of the CV and key information on the role of QPPV

The function of the QPPV at Stala Pharma is ensured by Dr. Patrícia Rodrigues, a pharmacist by background, who possesses the adequate pharmacovigilance training, knowledge and experience to fulfil this function.

The QPPV is registered in EudraVigilance (proof of registration is presented in Annex A) and has followed the relevant training courses on electronic reporting of ICSRs in the EU and on the Extended EudraVigilance medicinal product dictionary.

The QPPV is employed at Stala Pharma services and provides services to Stala Pharma Generics S.A. and Stala Pharma Products S.A.

2. Contact Details

Table 4 **- EEA QPPV**

QPPV: Patrícia de Lurdes Douteiro Rodrigues
Telephone: +351211122333
Telephone (24h): +351911122333
Fax: +351211122333
Address: Rua Alexandre Pinto, nº105, 3º esq, 2800-039 Lisbon, Portugal
Email: PhV@stalapharma.pt
Country: Portugal

3. Information relating to the contact person where such a person has been nominated at national level

Patrícia Rodrigues has also been nominated at national level, in Portugal, as a contact person for pharmacovigilance in accordance with article 104 (4) of Directive 2001/83/EC.

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Section II

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II.B.4.2. Organisational structure

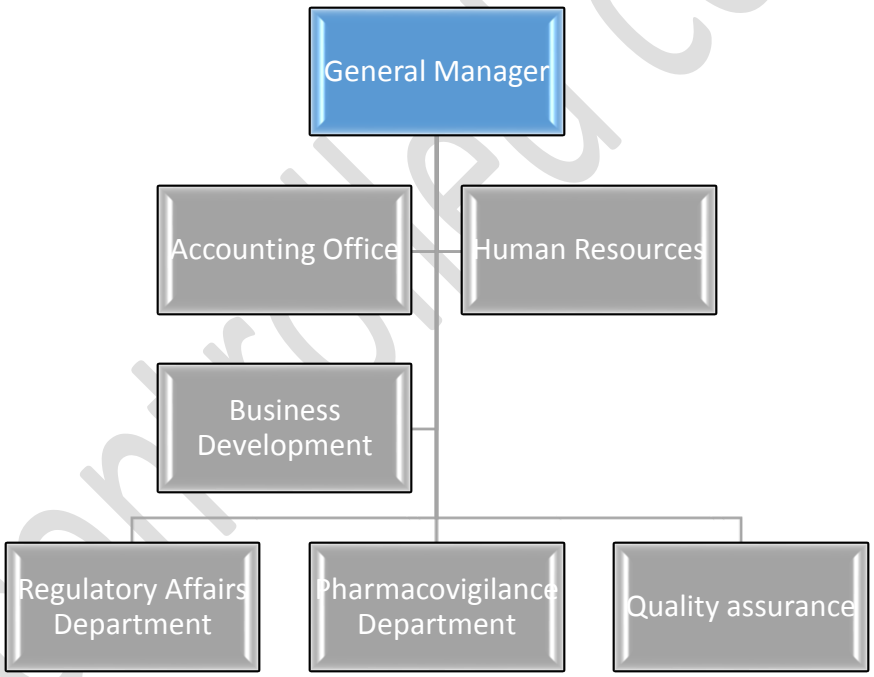
1. Description of Stala Pharma Group

The Stala Group is composed by the following companies:

1. Stala Pharma - Pharmaceutical Products, S.A.
2. Stala Pharma - Generics, S.A.
3. Stala Pharma – Services, Lda.

The Stala Pharma - Pharmaceutical Products, S.A. and the Stala Pharma - Generics, S.A. are Marketing Authorisation Holders and share the same Pharmacovigilance Master File.

The **Organisational Chart of Stala Pharma** is presented below:



The Stala Pharma – Services is an internal service provider operating under the same person's authority, the Managing Director.

2. Qualified Person for Pharmacovigilance and Deputy QPPV

The QPPV and Deputy QPPV are both employees of Stala Pharma – services. They fulfil the QPPV and Deputy Position for the companies within the group: Stala Pharma - Pharmaceutical Products, S.A. and the Stala Pharma - Generics, S.A.

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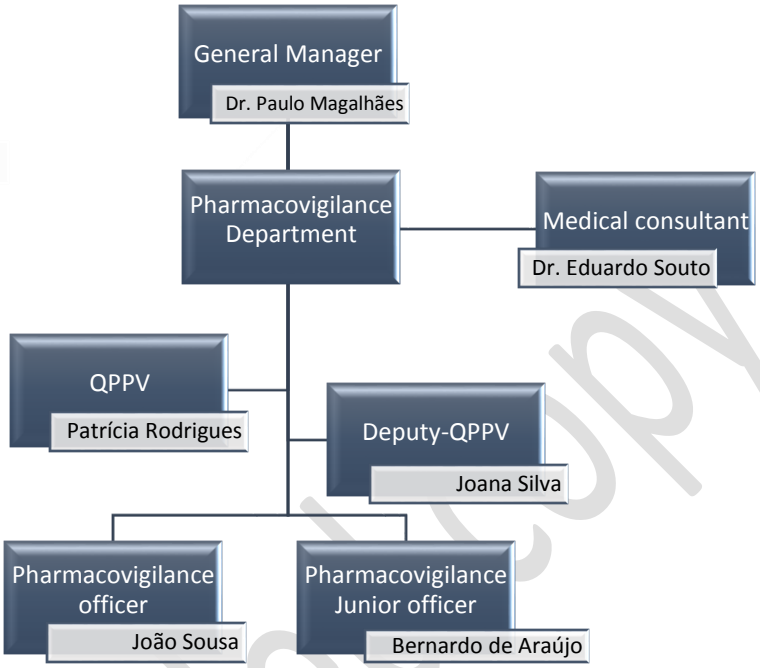
The Pharmacovigilance Department is constituted by the QPPV, Deputy QPPV, Pharmacovigilance Officer and Pharmacovigilance Junior Officer.

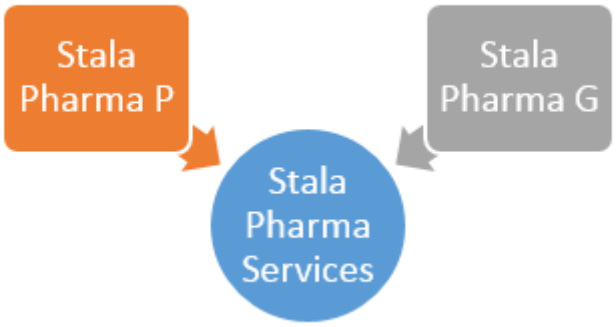
Organogram of **Pharmacovigilance Department**



3. Conduct of the Pharmacovigilance Activities

The Pharmacovigilance activities and processes are conducted at only one location, where the Pharmacovigilance System Master File (PSMF) as well as the EU QPPV and Deputy are located.

Stala Pharma Services centralises the fulfilment of the Pharmacovigilance activities for the companies of the group, as can be found in the following diagram:



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Nevertheless, there are some exceptions. The collection of ICSRs is performed by each of companies of the group. The delegated tasks listed in annex A as well as the auditing of the Pharmacovigilance master file that is performed by an independent contractors or by internal auditor who is independent from the Pharmacovigilance Department.

3.1. Collection of ICSRs

The collection of ICSRs is performed by each company of the group Stala Pharma including Stala Pharma Services as well as the partners listed in Annex A.

3.2. All other Pharmacovigilance activities

Except for the delegated tasks (as listed in annex A), Stala Pharma Services, in the person of both the QPPV and Deputy-QPPV, undertakes all the Pharmacovigilance activities for the group namely:

- Case processing and evaluation;
- Data entry in the safety database;
- Case submission to the regulatory authorities;
- Periodic safety update report management and preparation;
- Signal detection and analysis;
- Risk management plans management and preparation;
- Management of Safety Data Exchange Agreements;
- Pre and post-authorisation study management;
- Management of Pharmacovigilance audits and inspections;
- Etc…

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Section III

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II.B.4.3 The sources of safety data

1. Sources of safety information

The safety information at Stala Pharma can provided from:

- Spontaneous Reporting Systems (by health professionals, manufacturers, sales representatives or directly by patients);
- National PV Centre / Competent Authority;
- Published scientific literature and Drug Bulletins;
- Safety database;
- Media;
- Study results;
- Foreign Regulatory Agencies;
- Technical product complaints.

2. Overview of routes for collection of safety information

Safety information can be collected and reach the Pharmacovigilance Department at Stala Pharma by the following routes:

- Any employee at Stala Pharma Group;
- Consumers or patients (reporting by phone or email);
- Internet;
- Affiliate;
- Partner/Distributor.

A comprehensive list with the respective contacts can be found in Annex C.

3. Sources of individual case safety reports

The collection of safety information is done by all of the companies which take part in Stala Pharma Group (as described in section 2, Organizational Structure) as well as by the partners/distributors listed in Annex C**.**

In general, all employees are sources of potential safety information and are instructed to forward that information to the Pharmacovigilance department within 24 hours.

The pharmacovigilance mailbox address (phv@stalapharma.pt) as well as the telephone and mobile numbers of the QPPV and Deputy are provided to all upon training and are available on the company's intranet.

3.1. Unsolicited Reports

3.1.1 Spontaneous Reports

- Unsolicited communication of ADRs;
- By health care professionals or consumers;
- In a patient who was given one or more medicinal products;

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- do not derive from a study or any organized data collection scheme;
- is “voluntary” reporting;
- will not provide rates and incidences of ADRs.

3.1.2 Literature

The pharmacovigilance Department is responsible for regularly to screen the worldwide scientific literature by accessing widely used systematic literature reviews or reference databases. The frequency of the literature searches is every week.

3.1.3. Internet

Stala Pharma has a website where any person can consult the contacts and information regarding their products placed on the market. There is also the possibility of registering any suspicion of ADR. The pharmacovigilance Department should regularly screen this website for checking any potential ADR case reports.

3.1.4. Other Sources

If Pharmacovigilance Department at Stala Pharm Group becomes aware of a case report from non-medical sources, e.g. the lay press or other media, it should be handled as a spontaneous report.

3.2. Solicited Sources

Solicited reports are those derived from organized data collection systems, which include clinical trials, registries, post-approval named patient use programs, other patient support and disease management programs, surveys of patients or healthcare providers, or information gathering on efficacy or patient compliance. In this moment there is not a study.

3.3 Contractual Agreements

Stala Pharm Group takes place through contractual agreements between different distributors/partners, which market the same product in different countries/regions.
The Safety Data Exchange Agreements (SDEA) has been established between the different distributors. The timelines and processes for exchange will vary per partner but the collection and adequate processing of information is safeguarded.

3.4 Regulatory Authority Sources

Cases with regulatory origin are received directly by the Pharmacovigilance department mailbox.

4. Processing of safety information

Processing and reporting of safety information is always done by the QPPV and/or Deputy QPPV, unless otherwise agreement upon via a SDEA.

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Section IV

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B.II.4.4. Computerized Systems & Databases

1. Computerized Systems and their purpose

The department of pharmacovigilance at Stala Pharma has a significant number of computerized systems to support the performance of its activities. Further information with regards to the systems in place can be found in annex D.

1.1 Processing of safety information

The database used to manage the ADRs was built on an excel spreadsheet and is inserted in the documental system **Spotyver Plus.** The access to this excel spreadsheet is blocked by a password and is only accessible by the pharmacovigilance department.

1.2 Processing of other safety related information

RegistMed is a system used to register incoming contacts in relation to medical information requests or enquiries, pharmacovigilance information or reports, product quality or technical complaints.

1.3 Aggregate Reporting

The structure of the PSUR is developed by using the **eCTD Manager** and their submission is made by the **eSubmission Webclient** (the tool made available by the EMA).

Pharmacovigilance cases are submitted to the Agency through the **EudraVigilance system**, which is a thematic network allowing the exchange of pharmacovigilance data capable of producing XLM files and receiving confirmation messages.

All additional documents are submitted to the competent authority/partners/distributors through the **Eudralink**, in order to ensure the confidentiality of the transmission.

1.4 Document Management

Spotyver Plus is the system used to manage and control documents within Stala Pharma Group. The life cycle of the documents is controlled via **Spotyver Plus** allowing a transparent generation, revision, approval, update, access, storage and discontinuation of documents within the Stala Pharma Group.

All documents which are part of the PSMF are also stored and controlled within **Spotyver plus**.

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1.4 Product information

The submission and update of product information into the XEVMPD is done by the EV Webtrader (system made available by the EMA).

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Section V

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B.II.4.5. Pharmacovigilance Process

A Quality Management System, with relevant procedures and processes, is in place in order to ensure the following:

- The continuous monitoring of pharmacovigilance data, the examination of options for risk minimisation and prevention and appropriate measures are taken by Stala Pharma;
- The scientific evaluation by Stala Pharma of all information on the risks of their medicinal products;
- The submission of accurate and verifiable data on serious and non-serious adverse reactions to the Eudravigilance database;
- The quality, integrity and completeness of the information submitted on the risks of medicinal products, including processes to avoid duplicate submissions and to validate signals;
- Recording and traceability of the information;
- Effective communication by Stala Pharma with national competent authorities and the agency, including communication on new risks or changed risks, the PSMF, risk management systems, risk minimisation measures, periodic safety update reports, corrective and preventive actions, and post-authorisation studies;
- The update of product information by Stala Pharma in the light of scientific knowledge, including the assessments and recommendations made public via the European medicines web-portal, and on the basis of a continuous monitoring by Stala Pharma of information published on the European medicines web-portal;
- Appropriate communication by Stala Pharma of relevant safety information to healthcare professionals and patients.

Each pharmacovigilance procedural document is described in the annex E.

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Section VI

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B.II.4.6 Pharmacovigilance System performance

1. **The evaluation system used to assess the correct reporting of ICSRs**
   The assessment of reporting requirements of ICSR is conducted within the Pharmacovigilance department.

   Compliance figures with reporting timelines are provided in Annex F.

2. **The metrics used to monitor the quality of submissions and performance of pharmacovigilance**
   Compliance figures with reporting timelines are provided in Annex F.

3. **How PSUR submission to authorities is monitored**
   The management of the PSUR schedule is the responsibility of the Pharmacovigilance department.

   The PSUR schedules (Excel based), one for each company of Stala Pharma, are prepared by one member of the Pharmacovigilance department. The schedules are updated according to the current legislation and are reviewed on a monthly basis.

   Compliance figures with reporting timelines are provided in Annex F.

4. **How variation submissions are monitored**
   Compliance figures with reporting timelines are provided in Annex F.

5. **How Risk Management Plans Commitments, if any, are monitored**

   There is a database used to manage RMP and the respective commitments. This database is verified at least on a yearly basis and the fulfilment of the described commitments is checked against what has been implemented.

6. **Other metrics used to evaluate the performance of the system**.

Compliance figures with reporting timelines are provided in Annex F.

In accordance with Article 9 of commission implementing Regulation No. 520/2012 Stala Pharma uses performance indicators to evaluate the performance of the system. In Stala Pharma's PSMF a list of performance is present in annex F. The list is composed by the following indicators:

- ADR/AE input management
- Management of valid ADR
- Literature Research
- PSUR

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- Risk Management Plan (RMP)
- Safety variations
- Security measures

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Section VII

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B.II.4.7 Quality system

"The Quality System (QS) is part of the PV system and consists of its own structures and processes. It shall cover organisational structure, responsibilities, procedures, processes and resources of the pharmacovigilance system as well as appropriate resource management, compliance management and record management (IR Art 8(2))…"

1. **Document and Record control**

Pharmacovigilance documents and records are kept in two formats: electronically and in paper.

For pharmacovigilance processes, a database is used as the main document management system for electronic documents. It allows document search, document archive, requests for changes to documents in effect and the full audit trail of the document life cycle namely author, reviewers, approvers, document owner, changes made or requested to the documents, respective dates, etc...

The documents Summary of the Applicant's Pharmacovigilance System are archived electronically and in paper. The electronic format is maintained and controlled with Spotyver Plus and it was approved by the general director.

All documents which are part of the PSMF are controlled documents with Spotyver Plus.

The back-up of all documents available electronically is ensured via the back-up of the the servers at Stala Pharma Group.

The hard copy of the pharmacovigilance related documents are archived in the aforementioned locked cabinets with restricted access.

Recording all the information of PhV, handled and stored in such a way they can be reported, interpreted and verified thoroughly.

Pharmacovigilance data and documents relating to individual medicines authorized preserved as required.

Records management system for all documents used for pharmacovigilance activities are in place in order to:

- Easily find these documents;
- Track how and when were examined/made decisions on safety issues;
- Tracking and follow-up of adverse reaction reports;
- Keeping the elements of the PSMF according to law requirements.

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2. Procedural documents

A complete overview of procedural documents can be found in annex E – List of Procedural Documents.

With respect to procedural documents, the Quality Management System of Pharmacovigilance is integrated in the Stala Pharma Quality System.

The management of pharmacovigilance procedural documents is done Spotyver plus.

There are currently four of pharmacovigilance procedural documents:

1. SOPs: standard operating procedures describing in detail the who, what, how and when of the pharmacovigilance processes are performed;

2. Summary of the Applicant´s Pharmacovigilance System: documents describing in summary the pharmacovigilance system of all Marketing Authorisation Holders of Stala Pharma.

3. Pharmacovigilance system master file
Documents regarding pharmacovigilance system master file and the respective annexes.

4. Templates
Models to be used in pharmacovigilance activities.

All these documents are version controlled, have a reference number, an effective date, document owner, document approver and are entered in the database. The revision of existing procedures or triggering of the process for the implementation of new ones, is mainly of the responsibility of the Pharmacovigilance Department. Nevertheless, there are some situation where the responsibility is from another department listed in annex E.

3. Training

Organization chart and clear definition of roles and responsibilities (function in charge of PhV system implementation and oversight, execution, audit activities) is present in section 2 – Organisational Structure.

At Stala Pharma, clearly defined roles, job descriptions and training documented are available for all individuals.

An appropriate SOP describes in full detail the principles and processes for training of all staff members in pharmacovigilance matters.

The initial training of any new employee of Stala Pharma must include introductory training in pharmacovigilance.
Defined procedures to be followed in case of emergency (back up) must be in implemented at the beginning.

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The archive of training documentation is maintained in a specific area under the responsibility of Human Resources.

All pharmacovigilance employees must have Initial, documented and continuing training.

Pharmacovigilance training can be provided at the office in Lisbon or on another location, depending on the number of attendees and goal of the training.

4. Auditing

The process for audit planning, budgeting, fulfilment, correction and prevention of non-compliances, and follow-up auditing as well as the different types of audits that can be conducted and the risk based approach is described in appropriate SOP.

Periodic audits based on risk and process analysis, with a defined audit PLAN allow: to ensure compliance with quality system requirements described; to determine the effectiveness and outsourced activities covered by audit plan.

Annex G provides the strategic and the tactical audit programme, the overview of audits completed and the notes on previous significants' findings (graded critical and major) that are currently unresolved or not yet independently verified.

5. CAPA management

Defined SOPs to track, manage and periodically review corrective and preventative actions, to be reported to senior management in management review.

Deviation form is also used to determine the corrective action to be implemented as well as the staff responsible for that implementation.

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Annexes

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Annex A

1. Curriculum Vitae of QPPV Person

PATRÍCIA RODRIGUES

AVENIDA DA LIBERDADE, 58 – 2ºDIR; 2850-963, LISBON - PORTUGAL

+ 351 91 22 33 444 ▪ douteiropatricia@gmail.com

Date of birth: 02/01/1987
Nationality: Portuguese
Professional License Number: 18343
Pharmaceutical Order Number – Portuguese Pharmaceutical Society: C-03359
QPPV code (Eudravigilance): 58963 – Stala Pharma – Produtos farmacêuticos, S.A.

WORK EXPERIENCE

Qualified Person for Pharmacovigilance (QPPV)
Stala Pharma - Pharmaceutical Products, S.A. ▪ October 2016 – present ▪ Lisbon, Portugal

Pharmacovigilance Officer
Phagesson - Pharmaceutical Services and Consulting ▪ January 2015 – September 2016 ▪ Lisbon, Portugal

Global Project Manager, Pharmacovigilance
UBP - An Express Scripts Company▪ October 2013 – December 2014 ▪ Genève, Switzerland

Regulatory affairs officer
Grupo Tecnipharma ▪ September 2010 - September 2013- Lisbon, Portugal

ADDITIONAL INFORMATION – TRAINING

Training course: (15 hours) Nov 15 - Pharmacovigilance Intensive Couse

Training Course workshop (8 hours) Nov 15 – Quality Management at Pharmacovigilance

Training Course (8 hours) Jun 15 MSSO – Coding with MEdDRA

Training Course (8 hours) Jun 15 MSSO – MedDRA safety Data Analysis and SMQs

Training Course (1 hours) Jun 15 EXTEDO – get ready for the 2014 XEVMPD Requirements

Training Course: webinar Jun 15 EXTEDO – adverse event reporting: requirement of a contact person for pharmacovigilance and how to effectively manage your cases

Training Course: webinar September 2014 - EMA: training sessions on e-submission Gateway and web client for PSUR single-assessment submissions

Training Course: (2 hours) Aug 15 MSSO- Introduction to MEDdra Dictionary

Training Course: (3 days) July 14- Eudravigilance – Electronic Reporting of ICSRs in the EU attendance and approval

Training Course: (2 days) Nov 14 - DIA- Extended Eudravigilance Medical Product Dictionary Attendance and Approval

EDUCATION AND TRAINING University of Lisbon, Faculty of pharmacy
2014 ▪ Master's degree, Regulation and Evaluation of Medicines and Health Products

University of Coimbra, Faculty of pharmacy
2005-2010 ▪ Master, Pharmaceutical Sciences

PERSONAL SKILLS

Mother tongue(s): Portuguese

Other Language(s):

	Understanding		**Speaking**		**Writing**
	Listening	Reading	Spoken interaction	Spoken production	
English	B2	B2	B2	B2	B2
Spanish	B2	B2	B2	B2	B1
France	B2	B2	B2	B2	B2

Levels: A1/2: basic user – B1/2: independent user – C1/2 Proficient user
Common European Framework of Reference for Languages

Computer skills: good informatics knowledge as user

Driving license: Type B

2. Curriculum Vitae of Deputy-QPPV Person

Curriculum Vitae

Joana Silva

+351 91 9988777 # Joana.silva@gmail.com

EXPERIENCE

Qualified person for Pharmacovigilance Deputy (QPPV Deputy) at STALA PHARMA
▪ 10/2016 – Present ▪ Lisbon

Pharmaceutical Affairs Officer at Sandiz Farmacêutica, Lda
▪ 02/2015 – 09/2016 ▪ Lisbon

Pharmacovigilance trainee at Medincinfa
▪ 07/2014 – 01/2015 ▪ Lisbon

EDUCATION AND TRAINING

University of Lisbon, Faculty of Medicine
2015 ▪ Intensive course of Pharmacovigilance

University of Lisbon, Faculty of pharmacy
2014 ▪ Master, Pharmaceutical Sciences

EDUCATION AND TRAINING

University of Lisbon, Faculty of Medicine
2015 ▪ Intensive course of Pharmacovigilance

University of Lisbon, Faculty of pharmacy
2014 ▪ Master, Pharmaceutical Sciences

	Understanding		**Speaking**		**Writing**
	Listening	Reading	Spoken interaction	Spoken production	
English	B2	B2	B2	B2	B2

Levels: A1/2: basic user – B1/2: independent user – C1/2 Proficient user
Common European Framework of Reference for Languages

Computer skills: good informatics knowledge as user

Driving license: type B

3. Proof of registration with Eudravigilance

3.1. Proof of registration of the QPPV

Table 5 - QPPV Users List

Organization ID	Organization	Organisazion Type	QPPV		QPPV Code	Products as QPPV
			First Name	Family Name		
Stala Pharma P		Affiliate	Patrícia de Lurdes	Douteiro Rodrigues	58963	4
Stala Pharma G		Affiliate	Patrícia de Lurdes	Douteiro Rodrigues	58963	4

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3.2 Proof of registration of Stala Pharma

Organization Information

Organization Name: STALA PHARMA PHARMACEUTICAL PRODUCTS, SA.

Organisation identifier:

Trademark:

Street: Rua Alexandre Pinto, nº105, 3º Esq ,

City: Lisbon

Postal code: 2800-039

Area/state: Lisbon

Country: Portugal

Organization Name: STALA PHARMA GENERICS, SA.

Organisation identifier:

Trademark:

Street: Rua Alexandre Pinto, nº105, 3º Esq.,

City: Lisbon

Postal code: 2800-039

Area/state: Lisbon

Country: Portugal

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4. List of Delegated Tasks

4.1. Overview of delegated tasks by the QPPV

4.1.1. Internal delegation

Table 6 - list of internal delegation

Task	Execution	Revision on and by	Delegation
Fulfillment of the QPPV function	QPPV	-	Deputy QPPV
Preparation and submission to the authorities of PSURs addendum clinical overview and RMPs	QPPV/Deputy QPPV/PV Officer	Medical Consultant	-
Literature search	Deputy QPPV/PV officer/PV Junior Officer	Deputy Consultant	QPPV
Preparation and submission to the authorities: ICRs	QPPV/Deputy QPPV/PV Officer	Medical Consultant	-
Preparation of company-sponsored PASS	QPPV	Medical Consultant	Deputy QPPV
Overview of the safety profiles and any emerging safety concerns for the Stala Pharma's drugs	QPPV		Deputy QPPV/PV Officer
Provision of PhV training to the sales force	QPPV		Deputy QPPV/PV Officer
Provision of PhV training to third country/distributors	QPPV		Deputy QPPV
Management and submission of safety variations	QPPV	Regulatory Director	Deputy QPPV/Regulatory affairs department/PV Officer/PV Junior officer
Management of post-Authorization commitments (regarding PhV issues)	QPPV	Regulatory affairs department	Deputy QPPV/PV Officer
Preparation and management of safety agreements	QPPV	Business development Department	--
Monitoring the list published by EMA and security information	Deputy QPPV/PV Officer/ PV Junior Officer	-	QPPV

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4.1.2. External delegation

Table 7- List of external delegation

Delegated to	Task	Product (s)	Active substance
Medion Farmaceutici S.A. Via S.P. Cototoinego, 20 56394 Milano	- Undertaking signal detection. - To screen scientific literature. -Responsible for the development of PSURs and PBRER.	Primax 24 mg capsules	Mesoglycan
Abata Laboratories Lda Estrada da luz nº67 Betapark, Edifício E, Alcabideche 2696-365 Amadora	-Abata is responsible for conducting worldwide literature review and local medical literature. -Abata is responsible for signal detection. -Abata is responsible for development of PSURs.	Catalup 200 mg capsules	Fenofibrate

4.1.3. Delegation to Distributors

In cases where Stala Pharma Group is the marketing authorization holder, the pharmacovigilance department delegates tasks which are described in the field partner characterization/Delegated tasks.

It can be found in the next page.

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Table 8- Delegation activities to distributors

Country	Marketing authorisation Holder	Partner/distributor	Product	AIM date	Generics	Delegated tasks	Agreement
Morocco	Stala Pharma G	Morocco Distribution Ltd	Paracetamol MG 500 mg Tablet	4-12-2015	Yes	- National bibliographic search - Trainee in pharmacovigilance - Collecting and submitting ICRS	Agreement number "1256"
Mozambique	Stala Pharma P	Mozanpharma S.A.	Rufen, ibuprofene, 600 mg, film-coated tablets	6-01-2016	No	- National bibliographic search - Trainee in pharmacovigilance - Collecting and submitting ICRS	Agreement number "1255"

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5. Job description on Deputy-QPPV

Table 9 - Function: ***Deputy - QPPV***

Framework
OVERVIEW DESCRIPTION
The main focus of the Deputy QPPV is to support the EU QPPV by fulfilling its role and responsibilities in order to ensure complete oversight of the Stala Pharma Pharmacovigilance System in terms of its structure and performance. The deputy QPPV must reside in the EEA and be available 24h/7 days per week.
Competency requirements for the function performance
Educated to Degree Level (Degree in Pharmacy, Life Sciences degree, PhD or equivalent education).
Training and skills:
Understands and maintains knowledge of PV regulations and guidelines. Understanding of the regulatory processes. Proven Pharmacovigilance experience, in particular in leading safety affiliate roles. Strong organizational and time management skills. Flexibility and ability to prioritize and manage multiple tasks in a challenging environment. Excellent communication skills. Highly proactive, self-motivated, professional and dedicated. Excellent written and speaking skills in English; other languages as an asset. Proficient PC skills: MS Office Suite including PowerPoint , Excel, Word and Outlook at intermediate level
Experience Experience Minimum of 1 year working in Pharmacovigilance.
Description of the main responsibilities
1. Maintain the oversight of audits and PSUR quality and support the timely production and quality of the PSMF.
2. Review and comments safety reports as PSURs, RMPs, PASS protocols and other scientific documents on behalf of the EU QPPV and with regard to quality, accuracy and scheduling.
3. Assume the responsibilities of the EU QPPV when absent
4. Have oversight, with the EU QPPV and relevant functions, of all safety-related matters pertaining to AAA products having a potential impact on EU and EEA and supports the monitoring of cumulative safety data, potential safety signal detection activities, evaluation of the benefit/risk profile, decisions on labelling changes, development of Pharmacovigilance plans and risk minimization plans.
5. Support meetings with all affiliates, subcontractors and distributors.
6. Meet regularly with the EU QPPV to ensure that there is adequate information exchange.

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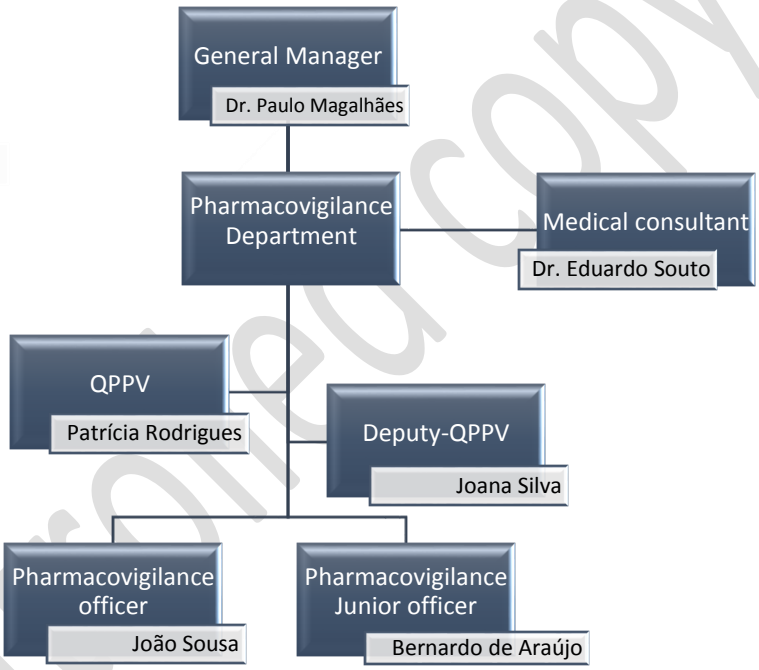
7. Fulfill any of the tasks of the EU QPPV as delegated
8. Keep up-to-date with the relevant PV regulations and all PV policies and procedures of the company.
9. Keep up-to-date with any changes to the global and European pharmacovigilance legislation and inform the department of any findings.
10. Manage the process of case report validation and deadline for competent authority.
11. Participate to audit to PV subcontractor, to initiate and follow up of all contracts with PV impact and to the validation of SmPC
ORGANOGRAM 
Remarks
This function can be performed in the technician category. The functions described as corresponding only to nuclear performed on this date and it can be subject to change at any time.
Function Holder Name: Joana Silva Signature: *Joana Silva* Date: 1/10/2016

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6. Job description on QPPV

Table 10 - Function: ***QPPV***

Framework	
OVERVIEW DESCRIPTION	
A QPPV has a central role focused on ensuring that the company meets all of its Pharmacovigilance responsibilities and that ultimately the safety of the public using the medicine is maximized. To have an overview of the safety profile for the products for which the company holds a Marketing Authorization. To implement and maintain a good Pharmacovigilance system. It is vital that the QPPV is available as a central point of contact to the competent authorities on a 24 hour basis and that an equally qualified and experienced deputy QPPV is appointed who can be contacted in their absence. The QPPV must reside in the EEA.	
Competency requirements for the function performance	
Education: degree in Medicine or Pharmaceutical Sciences with access to a doctor.	
Training and skills:	
Specific training in Pharmacovigilance, or practical experience proven. Good knowledge of the laws and regulations applicable to Pharmacovigilance. Good computer skills in the perspective of the user. Regular knowledge of the English language. Registered in the EudraVigilance database as QPPV.	
Experience QPPV who is experienced in pharmacovigilance (typically Master's degree and minimum two years of full time practical experience in pharmacovigilance)	
Description of the main responsibilities	
1. Establishing and maintaining/managing the MAH's Pharmacovigilance	Deputy QPPV
2. The establishment and maintenance of a system which ensures that information referred to all suspected adverse reactions which are reported to the personnel of the Marketing Authorisation Holder, and to medical representatives, is collected and collated in order to be accessible at least at one point within the EU;	Deputy QPPV
3. Ensuring that there is a Detailed Description of PV Systems in place.	Deputy QPPV
4. Preparation of ICSRs (PSURs) and company-sponsored post-authorization safety studies (PASS).	Deputy QPPV
5. Continuous overall Pharmacovigilance evaluation during the post-authorization period.	Deputy QPPV

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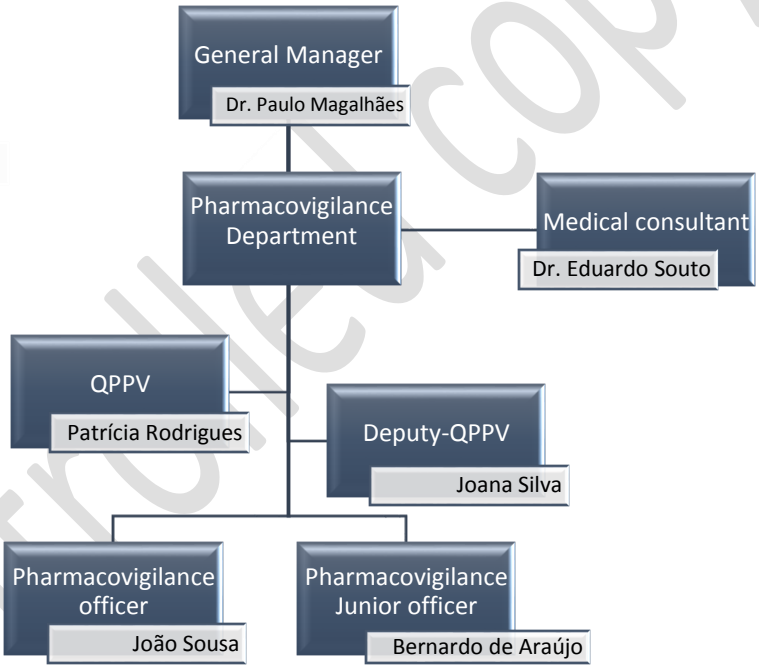
6. Ensure that any request from the health agency is fully and promptly answered.	
7. Have an overview of the safety profiles and any emerging safety concerns for the company's drugs.	Not delegate
8. Preparing Pharmacovigilance reports as defined by regulations such as ICSRs, PSURs, PASS.	Deputy QPPV
9. The QPPV should also act as the Marketing Authorisation Holder's contact point for Pharmacovigilance inspections or should be made aware by the Marketing Authorisation Holder of any inspection, in order to be available as necessary.	
10. The provision to the Competent Authorities of any other information relevant to the evaluation of the benefits and risks afforded by a medicinal product	Deputy QPPV
11. Participation on the performance of the risk plan management	Deputy QPPV

ORGANOGRAM



Remarks

This function can be performed in the technician category.
The employee who performs the QPPV function has sufficient authority to influence the system of quality management of Phv, as well as system and performance of Phv activities.
The functions described as corresponding only to nuclear performed on this date and it can be subject to change at any time.

Function Holder

Name: Patrícia de Lurdes Douteiro Rodrigues

Signature: *Patrícia de Lurdes Douteiro Rodrigues*

Date: 1/10/16

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Annex B

1. List of Contracts and Agreements

1.1. Internal contracts within the Stala Pharma Group.

Table 11 - List of delegation activities

From	To	PhV Agreement	Concerning about
Stala Pharma P	Stala Pharma Services	Agreement number 4521	All activities relating to: - Individual case safety report collection; - Evaluation; - Safety database case entry; - Periodic safety update report production; - Signal detection and analysis; - Risk management plan management; - Pre- and post-authorisation study management; - Management of safety variations to the terms of a marketing authorisation.
Stala Pharma G	Stala Pharma Services	Agreement number 4252	All activities relating to: - Individual case safety report collection; - Evaluation; - Safety database case entry; - Periodic safety update report production; - Signal detection and analysis; - Risk management plan management; - Pre- and post-authorisation study management; - Management of safety variations to the terms of a marketing authorisation.

1.2. External Contractual Partners

This contracts and agreements are performed and managed by a specific department (Business development). They have a particular site where the QPPV can access at any moment.

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Annex C

1. List of affiliates and third party contacts

1.1 Companies within the Stala Pharma Group

Table 12 - list of contacts

Company	Address	Phone contact	e-mail
Stala Pharma - Pharmaceutical Products, S.A.	Rua Alexandre Pinto, nº105, 3º esq, 2800-039 Lisbon – Portugal	+351 21 458 963	products@stalapharma.pt
Stala Pharma - Generics, S.A.	Rua Alexandre Pinto, nº105, 3º esq, 2800-039 Lisbon – Portugal	+351 21 458 963	generics@stalapharma.pt
Stala Pharma - Services, S.A.	Rua Alexandre Pinto, nº105, 3º esq, 2800-039 Lisbon – Portugal	+351 21 458 963	services@stalapharma.pt

1.2 Partners

Table 13 - list of contacts of partners

Company	Address	Phone contact	e-mail
Medion Farmaceutici S.A.	Via S.P. Cototoinego, 20 56394 Milano	+39 02 5953 6599	productsfarma@medion.it
Abata Laboratories Lda	Estrada da luz nº67 Betapark, Edifício E, Alcabideche 2696-365 Amadora	+351 414 466 431	products@abatalaboratories.pt

1.3. Distributors

Table 14 - list of contacts of distributors

Country	Distributor	PhV contact	Partners characterization/delegated tasks	PhV observation
Morocco	**Morocco Distribution Ltd**	m.r.c.@morpharma.com	- Bibliographic search - Trainee in PhV - Send a list of all valid ICSR - Send to us all information/queries/request derived from the RA	Confirmation of the performing of the trainee in PhV
Mozambique	**Mozanpharma S.A.**	pik@tresitapharma.com	- Bibliographic search - Trainee in PhV - Send a list of all valid ICSR	Confirmation of the performing of the trainee in PhV

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			- Send to us all information/queries/request derived from the RA	

2. Collection of information – websites

2.1. Scientific literature reports

2.1.1. National

- bibliovigilance.com

2.1.2. International

- ncbi.nlm.nih.gov/pubmed

2.1.3. Monitoring of medical literature (EMA)

- Eudravigilance.ema.europe.eu

2.2. Stala Pharma website

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2. List of studies and programmes

A Post-Authorisation Safety Study (PASS) to evaluate de effectiveness of the implementation of risk minimisation measures (RMMs) of isotretinoin is on-going.

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Annex D

1. Overview of Computerized systems

Table 15 - Overview of Computerized systems

System	Functionality	Location	Validation Status	Validation document	Fit for purpose	Operational Responsibility	Chance control managed by	Chance control Document	Back-up
MS Excel®	Safety database to collection ICSRs	Local server, Lisbon Portugal	N/A	N/A	Yes	Microsoft Excel	Microsoft Excel representative	N/A	N/A
EudraVigilance	Reporting ICSRs to the Agency	EMA servers	N/A	N/A	yes	EMA	EMA	N/A	N/A
RegistMed	Database for storage and tracking of information received via Customer Care Service (SAC) namely, Medical Information requests or enquiries, product technical or quality complaints and individual Case Safety Report.	Local server, Lisbon Portugal	N/A	N/A	yes	Salesforce	Sales manager representative	N/A	N/A

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System	Functionality	Location	Validation Status	Validation document	Fit for purpose	Operational Responsibility	Chance control managed by	Chance control Document	Back-up
eCTD	-Generation of PSUR structure for electronic submission -Generation of RMP structure for submission -Generate the structure of all documents needed in PhV activities.	Local server, Lisbon Portugal	N/A	N/A	yes	Extedo	Extedo	N/A	Daily Weekly Monthly Yearly
eSubmission WebClient	Electronic submission of PSURs	EMA servers	N/A	N/A	yes	EMA	EMA	N/A	N/A
Spotyver Plus	Documental management system	Local server, Lisbon Portugal	Validate	Validate document	yes	CHRin Stala IT	CHRin Stala IT	MOD001	Daily Weekly Monthly Yearly
EV WebTrader	To perform and update of product information into the XEVMPD	EMA servers	N/A	N/A	yes	EMA	EMA	N/A	N/A

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2. Overview of Databases

Table 16 - overview of databases

Database	Functionality	Responsibility	Documents identification
Contractual partners	List of contractual and agreements with PhV impact Identification of agreements for the PSMF purposes	Business Department and Pharmacovigilance Department	Annex B (BII48.2 rev01) MOD1001
Affiliates and third party	List of affiliates and third party contracts	Regulatory Affairs Department and Pharmacovigilance Department	Annex C (BII48.3 rev01) MOD1002
Products	List of products covered by the PSMF	Regulatory Affairs Department	Annex H (BII48.8 rev01) MOD1003
PSUR and addendum to the clinical overview	Management of PSURs and Addendum to the clinical overview submission dates	Pharmacovigilance Department	MOD1004
Reconciliation data in PhV	Management of periodicity with partners for reconciliation purposes safety data exchanged during the concerned period of time	Pharmacovigilance Department	MOD1005
Signal management	Management of risks and safety signal. Source of information and the signal status (on going, under monitoring, closed). Scheduling of signal management reports. Existence of Risk Management Plan for each product.	Pharmacovigilance Department	MOD1006

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Database	Functionality	Responsibility	Documents identification
Procedures Deviations Management	Management of procedures deviations	Pharmacovigilance Department	MOD1007
Management of the information at XEVMPD	Management, submission and update of product information into the XEVMPD (according with article 57)	Pharmacovigilance Department	MOD1008
Safety Variations	Scheduling of safety variations submission dates Management of approval dates Identification of the person responsible for each safety variations Identification of the person responsible for each safety variation submitted	Pharmacovigilance Department	MOD1009
Bibliographic Search	Management of Bibliographic Search Identification of ICSRs or relevant information for each active substance marketed by Stala Pharma Group in literature	Pharmacovigilance Department	MOD1010

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Annex E

Pharmacovigilance Process and Written Procedures

The documented procedural documents include:

1. Standard operating procedures (SOPs)
2. Summary of the Applicant´s Pharmacovigilance System
3. Pharmacovigilance System Master File
4. Models

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1. Standard operating procedures (SOPs)

Table 17 - List of Standard operation Procedures

Name/version	Title	Date	Validity	Owner
PGE123rev03	Job description	09-10-2015	09-10-2018	Catarina Mendes Quality Person
PGE124rev05	Organization chart	09-10-2015	09-10-2018	Catarina Mendes Quality Person
PGE125rev01	Pharmacovigilance System Quality Management	01-10-2016	01-10-2019	Patrícia Rodrigues QPPV
PGE126rev10	Training	10-10-2016	10-10-2019	Catarina Mendes Quality Person
PGE127rev02	Research of Literature	10-10-2016	10-10-2019	Patrícia Rodrigues QPPV
PGE128rev03	Periodic safety Update reports	10-10-2016	10-10-2019	Patrícia Rodrigues QPPV
PGE129rev05	Signal Management and Risk-Benefit Evaluation	01-09-2016	01-09-2019	Patrícia Rodrigues QPPV
PGE130rev02	Pharmacovigilance System Master File Management	01-09-2016	01-09-2019	Patrícia Rodrigues QPPV

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Name/version	Title	Date	Validity	Owner
PGE131rev01	Risk Management Plan	01-09-2016	01-09-2019	Patrícia Rodrigues QPPV
PGE132rev03	Response to requests for information	01-09-2016	01-09-2019	Patrícia Rodrigues QPPV
PGE133rev03	Communication of relevant information	01-09-2016	01-09-2019	Patrícia Rodrigues QPPV
PGE134rev02	Management of solicited and unsolicited safety information	01-09-2016	01-09-2019	Patrícia Rodrigues QPPV
PGE135rev03	Safety variations	01-09-2016	01-09-2019	Patrícia Rodrigues QPPV

2. Summary of the Applicant's Pharmacovigilance System

Table 18 - List of Summary of the Applicant's Pharmacovigilance System

Name/version	Title	Date	Validity	Owner
PGE134rev02	Summary of the Applicant's Pharmacovigilance System **Stala Pharma - Pharmaceutical Products, S.A.**	01-09-2016	01-09-2019	Patrícia Rodrigues QPPV
PGE135rev03	Summary of the Applicant's Pharmacovigilance System **Stala Pharma - Generics, S.A.**	01-09-2016	01-09-2019	Patrícia Rodrigues QPPV

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3. Pharmacovigilance System Master File

Table 19 - List of PSMF'documents

Name/version	Title	Date	Validity	Owner
IIB41.1rev00	Cover page	01-09-2016	01-09-2019	Patrícia Rodrigues QPPV
IIB41.2rev00	Quality Person for Pharmacovigilance	01-09-2016	01-09-2019	Patrícia Rodrigues QPPV
IIB42rev00	Organisation Structure	01-09-2016	01-09-2019	Patrícia Rodrigues QPPV
IIB43rev00	The sources of Safety Data	01-09-2016	01-09-2019	Patrícia Rodrigues QPPV
IIB44rev00	Computerised Systems and Databases	01-09-2016	01-09-2019	Patrícia Rodrigues QPPV
IIB45rev00	Pharmacovigilance Process	01-09-2016	01-09-2019	Patrícia Rodrigues QPPV
IIB46rev00	Pharmacovigilance System Performance	01-09-2016	01-09-2019	Patrícia Rodrigues QPPV

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Name/version	Title	Date	Validity	Owner
IIB47rev00	Quality system	01-09-2016	01-09-2019	Patrícia Rodrigues QPPV
IIB48.1 rev00	Annex A - List of delegated tasks Annex A – CV of QPPV Annex A – CV of Deputy QPPV Annex A - Job description of QPPV Annex A - Job Description of Deputy QPPV Annex A – Proof of registration with EudraVigilance	01-09-2016	01-09-2019	Patrícia Rodrigues QPPV
IIB48.2 rev01	Annex B – List of contracts and agreements	01-09-2016	01-09-2019	Patrícia Rodrigues QPPV
IIB48.3 rev00	Annex C - List of affiliates and third party contacts Annex C – List of studies and programmes	01-09-2016	01-09-2019	Patrícia Rodrigues QPPV
IIIB48.4 rev00	Annex D- Overview of computerised systems and Databases Annex D – Overview of Databases	01-09-2016	01-09-2019	Patrícia Rodrigues QPPV
IIB48.5 rev00	Annex E – List of Procedural documents	01-09-2016	01-09-2019	Patrícia Rodrigues QPPV
IIB48.6 rev00	Annex F – List of performance indicators Annex F – Compliance with submission timelines – past year	01-09-2016	01-09-2019	Patrícia Rodrigues QPPV
IIB48.7 rev00	Annex G – List of all scheduled and completed audits (5-year history)	01-09-2016	01-09-2019	Patrícia Rodrigues QPPV
IIB48.9 rev01	Annex I – Logbook-Date, person, nature of the change Annex I – History of changes in Annex A-H	01-09-2016	01-09-2019	Patrícia Rodrigues QPPV

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4. Models

Models to be used in pharmacovigilance activities.

An overview of databases is identified in BIIB4.4 rev00 (Annex D- Computerised Systems and Databases).

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Annex F

Performance Indicators used in Stala Pharma pharmacovigilance system

Table 20 - list of indicators

Type of Performance Indicator	Performance Indicator
ADR/AE input management	▪ Rate (100%) of received ADR/AE ▪ Average time needed for validation decision
Management of valid ADR	▪ Rate (100%) of valid ADR/AE ▪ Rate (100%) of valid ADR occurred in EU ▪ Rate (100%) serious ADR ▪ Rate (100%) non-serious ADR ▪ Rate (100%) of compliance on notification process ▪ Rate (100%) of compliance on notification deadlines
Literature Research	▪ Rate (90%) of literature researches ▪ Rate (90%) of processed literature research cases ▪ Rate (90%) of valid ADR originated from literature research
PSUR	▪ Rate (100%) of compliance on PSUR submissions ▪ Rate (100%) of compliance on PSUR submission deadlines ▪ Average time needed for PSUR submission upon Data Lock Point (± Standard Deviation)
Risk Management Plan	▪ Rate (100%) of medical products with RMP ▪ Rate (100%) of RMP with “Risk minimization measures” ▪ Rate (100%) of compliance on RMP updates ▪ Rate (100%) of compliance on RMP updates deadlines
Safety variations	▪ Rate (100%) of safety variations ▪ Rate (100%) of compliance on safety variations submission deadlines
Security measures	▪ Number of security measures per year ▪ Number of DHCP per year

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Compliance with submission timelines – past year

The objective of this annex F is to present current results of performance assessment in relation to the indicators regarding 2016.

1. ADR/AE input management

The target for ADR/AE input management indicator was 100 % according to PGE129rev05.

Table 21 - Data for measurement of the performance indicator

Number of received ADR/AE	Time need for validation	Conformity
5	2 days	Complies

2. Management of valid ADR

The target for Management of valid ADR indicator was 100 % according to PGE129rev05.

Table 22 - Data for measurement of the performance indicator

Number of valid ADR/AE	Number of valid ADR in EU	Number of serious ICSRs	Number of non-serious ICSRs	ICSRs reported to the Authority	ICSRs reported to the Authority within the legal deadline	Result
2	2	-	2	2	2	100%

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Table 23 -Data for measurement of the performance indicator

Wordwide ID number	Day 0	Data of transmission to the authorities/ conformity	Way to transmission	ACK/conformity
Pt-stalapharma-2016-02-5236	06-02-2016	08-02-2016 complies	gateway	01 complies
Pt-stalapharma-2016-02-5237	02-09-2016	05-02-2016 complies	gateway	02 complies

3. Submission of PSURs (PSURs reporting timelines)

The target for submission of PSURs indicator was 100 %. The goal was reached in 2016.

Table 24 - Data for measurement of the performance indicator

Total od PSURs Scheduled in 2016	PSURs submitted	PSURs submitted within the legal deadline	PSURs reported with ACK 01	Result
2	2	2	2/2 (e-submission)	100%

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Table 25- Data for measurement of the performance indicator

Medicine	Data lock point	Date scheduled for submission	Data of submission to the authorities/ conformity	ACK (for e-submission)/conformity
Isotretinoin	06-05-2016	06-08-2016	07-08-2016	01 complies
Rufen	03-10-2016	03-11-2016	05-11-2016	01 complies

4. Submission of RMPs (RMP reporting timelines)

The target deadline for submission of RMPs was 100% according to PGE131rev01.

Table 26 - Data for measurement of the performance indicator

Total of RMPs Schedule in 2016	Medicinal product	RMPs submitted	RMPs submitted within the legal deadline	RMP with "Risk minimization measures"	Result
1	Paracetamol MG	1	1	No	100 %

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5. Safety variations (safety variations submitted within the legal deadline)

The target deadline for submission of safety variations indicator was 100 % according to PGE135rev03

Table 27 - Data for measurement of the performance indicator

Total of safety variations submitted in 2016	Safety variations submitted within the legal deadline	Result
3	3	100%

Table 28 - Data for measurement of the performance indicator

Medicine	Pharmaceutical form	Dosage	Variation type	Variation Type	Data scheduled for submission	Data of submission to the authorities/conformity
Rufen (Ibuprofeno)	Film-coated tablets	600 mg	IB	C.I.1.a)	12-02-2016	10-02-2016 complies
Omeprax (omeprazole)	Gastro-resistant capsules	20 mg	IB	C.I.z	11-05-2016	27-04-2016 Complies
Isotretinoína MG	Soft capsules	10 mg	IA_{IN}	C.I.8)	12-12-2016	27-04-2016 Complies

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6. Bibliographic Research (Bibliographic research performed within legal timelines)

The target for bibliographic research performed indicator was 90 % according to PGE127rev02

Table 29 - Data for measurement of the performance indicator

Number of literature researches	Number of processed literature research cases	Number of valid originated from literature cases	Result
52	10	10	100 %

7. Security measures

Table 30 - Data for measurement of the performance indicator

Number of security measures per year	Number of DHCP per year
1	1

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Annex G

1 Strategic Audit program

Table 31 - Strategic Audit program

2017 to 2021					
Auditee and /or process to be audited	**Level of risk**	**Justification for level of risk**	**Last audit date**	**Period to be covered**	**Products**
Mozanpharma S.A. - National bibliographic search -Trainee in pharmacovigilance - collecting and submitting ICRS	Low	Product market in Mozambique Stala Pharma is MAH of the products referred	Not applicable	January 2016 to (to be defined)	Paracetamol MG, 500 mg, tablet
Morocco Distribution Ltd - National bibliographic search -Trainee in pharmacovigilance -Collecting and submitting ICRS	Low	Product market in Mozambique Stala Pharma is MAH of the products referred	Not applicable	January 2016 to (to be defined)	Rufen, ubuprofene, 600 mg, film-coated tablets
Pharmacovigilance system and processes of Stala Pharma Group, including quality system for pharmacovigilance activities	High	Stala Pharma is the MAH and has to audit the system every 2 years.	December 2016	December 2016 to December 2018	All product which Stala Pharma is a MAH
Pharmacovigilance system and processes of Stala Pharma Group, including quality system for pharmacovigilance activities	High	Stala Pharma is the MAH and has to audit the system every 2 years.	Not know yet	December 2018 to December 2020	All product which Stala Pharma is a MAH

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Table 32- Strategic Audit program

2017 to 2021					
Auditee and /or process to be audited	**Level of risk**	**Justification for level of risk**	**Last audit date**	**Period to be covered**	**Products**
Medion Farmaceutici S.A. - Process for undertaking signal detection. - Process to screen scientific literature. - Process for the development of PSURs and PBRER.	High	Stala Pharma is MAH of the product referred	Not applicable	December 2017 to December 2019	Primax 24 mg capsules
Abata Laboratories Lda -Process for conducting worldwide literature review and local medical literature. -Process for signal detection. -Process for development of PSURs.	High	Stala Pharma is MAH of the product referred	Not applicable	December 2018 to December 2020	Catalup 200 mg capsules

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2. Tactical level audit planning – 1 year

Table 33 - Tactical level audit planning

Proposed dates	Duration	Auditee/process to be audited	Audit team	Confirmed by	Date of confirmation
December 2017	4 hours	- Process of National bibliographic search -Process of trainee in pharmacovigilance - Process of collecting and submitting ICRS	QPPV and Deputy-QPPV	Morocco Distribution Ltd	Not yet available
December 2017	4 hours	- Process of National bibliographic search -Process of trainee in pharmacovigilance - Process of collecting and submitting ICRS	QPPV and Deputy-QPPV	Mozanpharma S.A.	Not yet available

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Annex H - List of Products at Stala Pharma Group

Table 34 - List of medicinal products

Marketing authorisation Holder	Product name	Active substance	AIM date	Type of procedure	Generics	Brand	Risk management Plan	Product additional monitoring	Additional risk minimisation measures
Stala Pharma G	Paracetamol MG 500 mg Tablet	Paracetamol	4-12-2015	National	No	yes	yes	No	No
Stala Pharma G	Isotretinoin MG 10 mg Soft capsule	Isotretinoin	xx-xx-xxxx	National	yes	No	yes	No	Yes PPG
Stala Pharma P	Rufen 600 mg Film-coated tablet	Ibuprofene	6-05-2012	National	No	yes	Yes	No	No
Stala Pharma P	Omeprax 20 mg Gastro-resistant capsules	Omeprazole	6-04-2005	National	No	Yes	No	No	No

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Annex I

1. History of changes in Annex A-H

The contents of the annexes belonging to the Pharmacovigilance System Master File, from IIB4 up to IIB48, are inserted into the Documental Data Base.

The annexes listed in the table below show the last changes occurred in this Annex of PSMF.

Table 35 - List of last changes in Annexes

Annex of the PSMF	Name of document	Document	Location of the document	Location of the last copy	Responsible for the change
Annex C - List of affiliates and third party contacts	Export management	Doc123	Contract management, Doc123	Regulatory department	Susana Pinto
Annex B- List of contracts and agreements	List of contracts and agreements relevant to pharmacovigilance	Doc126	List of contracts and agreements relevant to pharmacovigilance, Doc126	Pharmacovigilance Department	Patrícia Rodrigues
Annex H – List of products	General map	Doc125	General map, Doc125	Regulatory department	Carla Paiva

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2. Logbook (Date, person, nature of the change)

The logbook is a detailed table where it is described all the main procedures in Pharmacovigilance, as well as the date, signature and the name of the person who did it.

If there were changes to the normal procedure, it is required justification and the identification of the collaborator.

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Risk management plan (RMP) for Isotretinoin

Content

EU Risk Management Plan for Isotretinoin Generics®

Isotretinoin

RMP version to be assessed as part of this application:

RMP Version number: 0.1

Data lock point for this RMP: 30-05-2017

Date of final sign off: 25-08-2017

Rationale for submitting an updated RMP: Not applicable

Summary of significant changes in this RMP: Not applicable

QPPV name: Patrícia de Lurdes Douteiro Rodrigues

QPPV signature: Patrícia de Lurdes Douteiro Rodrigues

Part I: Product(s) Overview

Table 36 - Part I.1 – Product Overview

Active substance(s) **(INN or common name)**	Isotretinoin
Pharmacotherapeutic group(s) (ATC Code)	D10BA01
Marketing Authorisation Holder	Stala Pharma Generics
Medicinal products to which this RMP refers	1
Invented name(s) in the European Economic Area (EEA)	Not applicable
Marketing authorisation procedure	National
Brief description of the product	**Chemical class** Isotretinoin belongs to the pharmacotherapeutic group of antiacne preparations for systemic use. Isotretinoin is a stereoisomer of all-trans retinoic acid (tretinoin).
	Summary of mode of action Its exact mechanism of action has not yet been elucidated in detail, but it has been established that the improvement observed in the clinical picture of severe acne is associated with suppression of sebaceous gland activity and a histologically demonstrated reduction in size of the sebaceous glands. Furthermore, a dermal anti-inflammatory effect of isotretinoin has been established.
Hyperlink to the Product Information	Isotretinoin Generics 10/0000/m1/eu/13-pi/13.1-pil/Portugal
Indication(s) in the EEA	Severe forms of acne (such as nodular and conglobate acne or acne at risk of permanent scarring) resistant to adequate courses of standard therapy with systemic antibacterial and topical therapy.

Dosage in the EEA	Isotretinoin should only be prescribed by or under the supervision of physicians with expertise in the use of systemic retinoids for the treatment of severe acne and a full understanding of the risks of isotretinoin therapy and monitoring requirements. Isotretinoin should only be prescribed by or under the supervision of physicians with expertise in the use of systemic retinoids for the treatment of severe acne and a full understanding of the risks of isotretinoin therapy and monitoring requirements. **Adults including adolescents and the elderly:** Isotretinoin therapy should be started at a dose of 0.5 mg/kg daily. The therapeutic response to isotretinoin and some of the adverse effects are dose-related and vary between patients. This necessitates individual dosage adjustment during therapy. For most patients, the dose ranges from 0.5-1.0 mg/kg per day. Long-term remission and relapse rates are more closely related to the total dose administered than to either duration of treatment or daily dose. It has been shown that no substantial additional benefit is to be expected beyond a cumulative treatment dose of 120-150 mg/kg. The duration of treatment will depend on the individual daily dose. A treatment course of 16-24 weeks is normally sufficient to achieve remission. In the majority of patients, complete clearing of the acne is obtained with a single treatment course. In the event of a definite relapse a further course of isotretinoin therapy may be considered using the same daily dose and cumulative treatment dose. As further improvement of the acne can be observed up to 8 weeks after discontinuation of treatment, a further course of treatment should not be considered until at least this period has elapsed. **Patients with renal impairment** In patients with severe renal insufficiency treatment should be started at a lower dose (e.g. 10 mg/day). The dose should then be increased up to 1 mg/kg/day or until the patient is receiving the maximum tolerated dose (see section 4.4). **Paediatric population** Isotretinoin is not indicated for the treatment of prepubertal acne and is not recommended in patients less than 12 years of age due to a lack of data on efficacy and safety. **Patients with intolerance** In patients who show severe intolerance to the recommended dose, treatment may be continued at a lower dose with the consequences of a longer therapy duration and a higher risk of relapse. In order to achieve the maximum possible efficacy in these patients the dose should normally be continued at the highest tolerated dose.

Pharmaceutical form(s) and strengths	Soft capsules 10 mg
Is/will the product be subject to additional monitoring in the EU?	No

Part II: Safety specification

Part II: Module SI - Epidemiology of the indication(s) and target population(s)

This module is not applicable for RMPs submitted with initial marketing authorisation applications involving Generic medicinal products. Isotretinoin Generics is a generic medicinal product, so this module is not applicable.

Part II: Module SII - Non-clinical part of the safety specification

This module is not applicable for RMPs submitted with initial marketing authorisation applications involving Generic medicinal products. Isotretinoin Generics is a generic medicinal product, so this module is not applicable.

Part II: Module SIII - Clinical trial exposure

This module is not applicable for RMPs submitted with initial marketing authorisation applications involving Generic medicinal products. Isotretinoin Generics is a generic medicinal product, so this application is not applicable.

Part II: Module SIV - Populations not studied in clinical trials

This module is not applicable for RMPs submitted with initial marketing authorisation applications involving Generic medicinal products. Isotretinoin Generics is a generic medicinal product, so this module is not applicable.

Part II: Module SV - Post-authorisation experience

This module is not applicable in the same situations as Module SIV, described above.

Part II: Module SVI - Additional EU requirements for the safety specification

Potential for misuse for illegal purposes

This module is not applicable in the same situations as Modules SIV-SV as described above.

Part II: Module SVII - Identified and potential risks

The originator product does not have an RMP but the safety concerns of the substance are published on the CMDh website, therefore this module is not applicable.

Part II: Module SVIII - Summary of the safety concerns

Table 37 - SVIII.1: Summary of safety concerns

Summary of safety concerns	
Important identified risks	Teratogenicity Psychiatric Disorders- including depression, suicidality and anxiety Eye disorders including corneal opacities, reduced night vision and keratitis Musculoskeletal and connective tissue disorders including bone changes and rhabdomyolysis Severe skin reactions (including SJS and TEN) Benign intracranial hypertension Severe increase in triglyceride levels, sometimes associated with acute pancreatitis Severe allergic reactions
Important potential risks	Gastrointestinal disorders including inflammatory bowel disease
Missing information	Not applicable

Part III: Pharmacovigilance Plan (including post-authorisation safety studies)

III.1 Routine pharmacovigilance activities

The routine pharmacovigilance is the primary set of activities required to fulfil the legal requirements for pharmacovigilance contained in Directive 2001/83/EC and Regulation (EC) No 726/2004.

All the routine pharmacovigilance activities for isotretinoin are performed by Stala Pharma following processes and procedures that are summarized in the current version of the Pharmacovigilance System Master File. This routine pharmacovigilance includes the following:

- Systems and processes that ensure that information about all suspected adverse reactions that are reported to the personnel of the company are collected and collated in an accessible manner;
- The preparation of reports for regulatory authorities:
    - o Expedited adverse drug reaction (ADR) reports;
    - o Periodic Safety Update Reports (PSURs).
- Continuous monitoring of the safety profile of approved products including signal detection, issue evaluation, updating of labelling, and liaison with regulatory authorities;
- Other requirements, as defined by local regulations.

III.2 Additional pharmacovigilance activities

In order to assist prescribers, pharmacists and patients, the Marketing Authorisation Holder provides educational materials to reinforce the warnings about the teratogenicity, psychiatric disorders including depression and severe lipids disorders including pancreatitis. Therefore, as an additional pharmacovigilance activity we propose a Post-Authorisation Safety Study (PASS) to evaluate de effectiveness of the implementation of these risk minimisation measures (RMMs).

The Planned pharmacovigilance activities by safety concerns are presented below:

- **Teratogenicity and drug exposure during pregnancy**

- Routine pharmacovigilance
- Enhanced pharmacovigilance

(Close monitoring, aggregate analysis in PSUR, signal detection, specific post-marketing notification form and documentation of cases)

- **Depression, suicide, suicide attempt, suicide ideation**

- Routine pharmacovigilance
- Enhanced pharmacovigilance

(Close monitoring, aggregate analysis in PSUR, signal detection, specific post-marketing notification form and documentation of cases)

- **Severe lipid metabolism disorders with acute pancreatitis**

- Routine pharmacovigilance
- Enhanced pharmacovigilance

(Close monitoring, aggregate analysis in PSUR, signal detection, documentation of cases).

III.3 Summary Table of additional Pharmacovigilance activities

Table 38 – Summary of additional PhV activities

Safety concerns	Planned Action (s)
Important identified risks	
Teratogenicity Psychiatric Disorders- including depression, suicidality and anxiety Severe increase in triglyceride levels, sometimes associated with acute pancreatitis	**Routine Pharmacovigilance** measures described above **Additional pharmacovigilance activities** In order to assist prescribers, pharmacists and patients, the Marketing Authorisation Holder provides **educational materials** to reinforce the warnings about the teratogenicity, psychiatric disorders including depression and severe lipids disorders

	including pancreatitis. Therefore, as an additional pharmacovigilance activity we propose a Post-Authorisation Safety Study (PASS) to evaluate de effectiveness of the implementation of these risk minimisation measures (RMMs) **Official title:** Evaluation of the Effectiveness of Risk Minimisation Measures: A Joint PASS Survey and Drug Utilisation Study among Health Care Professionals to Assess their Knowledge and Attitudes on Prescribing Conditions of isotretinoin in France, Germany, Portugal, Spain, Sweden and United Kingdom **Study type**: Observational study **Brief description of the study**: Evaluation of the Effectiveness of Risk Minimisation Measures: A Joint PASS Survey and Drug Utilisation Study among Health Care Professionals to Assess their Knowledge and Attitudes on Prescribing Conditions of isotretinoin in France, Germany, Portugal, Spain, Sweden and United Kingdom EU RMP category 3 (required) **Start date of data collection** 31/03/2016 to 31/08/2017 **Date of final study report** 09/09/2018
Severe skin reactions Eye disorders including corneal opacities, reduced night vision and keratitis Musculoskeletal and connective tissue disorders including bone changes and rhabdomyolysis	**Routine Pharmacovigilance** measures described above **Additional pharmacovigilance activities** Not applicable

Severe skin reactions (including SJS and TEN) Benign intracranial hypertension Severe allergic reactions	
Important potential risks	
Gastrointestinal disorders including inflammatory bowel disease	**Routine Pharmacovigilance** measures described above **Additional pharmacovigilance activities** Not applicable
Missing information	
Not applicable	**Routine Pharmacovigilance** Not applicable **Additional pharmacovigilance activities** Not applicable

Part IV: Plans for post-authorisation efficacy studies

Not applicable.

Part V: Risk minimisation measures (including evaluation of the effectiveness of risk minimisation activities)

Risk Minimisation Plan

V.1. Routine Risk Minimisation Measures (RMM)

Table 39 - Part V.1: Description of routine RMMs by safety concerns

Safety concern	Routine risk minimisation activities
Teratogenicity	Routine risk communication: Provide in SmPC section **4.3. Contraindications** Isotretinoin is contraindicated in women who are pregnant or breastfeeding (see section 4.6). Isotretinoin is contraindicated in women of childbearing potential unless all of the conditions of the Pregnancy Prevention Programme are met (see section 4.4). Provide in SmPC section **4.4. Special warnings and precautions for use** Pregnancy Prevention Programme This medicinal product is TERATOGENIC Isotretinoin is contraindicated in women of childbearing potential unless all of the following conditions of the Pregnancy Prevention Programme are met: - She has severe acne (such as nodular or conglobate acne or acne at risk of permanent scarring) resistant to adequate courses of standard therapy with systemic anti-bacterials and topical therapy (see section 4.1). - She understands the teratogenic risk, if becoming pregnant. - She understands the need for rigorous follow-up, on a **monthly basis**. - **A pregnancy test is mandatory in each follow-up visit**. - She understands and accepts the need for effective contraception, without interruption, 1 month before starting treatment, throughout the duration of treatment and 1 month after the end of treatment. **Two complementary forms of contraception** including a barrier method, e.g. a condom or a diaphragm, should be used. **Calendar-based contraceptive methods or Coitus interrupts shall not be used** due its lack of effectiveness. - Even if she has amenorrhea she must follow all of the advice on effective contraception. - She should be capable of complying with effective contraceptive measures.

	- She is informed and understands the potential consequences of pregnancy and the need to rapidly consult a doctor if there is a risk of pregnancy. - She understands the need and accepts to undergo pregnancy testing before, during and 5 weeks after the end of treatment. - She has acknowledged that she has understood the hazards and necessary precautions associated with the use of isotretinoin. These conditions also concern women who are not currently sexually active unless the prescriber considers that there are compelling reasons to indicate that there is no risk of pregnancy. **Contraception** Female patients must be provided with comprehensive information on pregnancy prevention and should be referred for contraceptive advice if they are not using effective contraception. As a minimum requirement, female patients at potential risk of pregnancy must use two effective method of contraception. Contraception must include a barrier method, and start at least 4 weeks before the treatment, during the treatment and should be continued for at least 1 month after stopping treatment with isotretinoin, even in patients with amenorrhea. Calendar-based contraceptive methods or Coitus interrupts shall not be used due its lack of effectiveness. Provide in SmPC section **4.6 - Fertility, pregnancy and lactation** Pregnancy Pregnancy is an ABSOLUTE contraindication to treatment with isotretinoin (see section 4.3). If pregnancy does occur in spite of these precautions during treatment with isotretinoin or in the month following, there is a great risk of very severe and serious malformation of the foetus. Even minimal doses of isotretinoin administered during very short periods, may have teratogenic effects. The foetal malformations associated with exposure to isotretinoin include central nervous system abnormalities (hydrocephalus, cerebellar malformation/abnormalities, microcephaly), facial dysmorphia, cleft palate, external ear abnormalities (absence of external ear, small or absent external auditory canals), eye abnormalities (microphthalmia), cardiovascular abnormalities (conotruncal malformations such as tetralogy of Fallot, transposition of great vessels, septal defects), thymus gland abnormality and

	parathyroid gland abnormalities. There is also an increased incidence of spontaneous abortion. If pregnancy occurs in a woman treated with isotretinoin, treatment must be stopped, and the patient should be referred to a physician specialised or experienced in teratology for evaluation and advice. Associated wording is included in the PIL. Labelling also warning about the risks of teratogenicity. *Other routine risk minimisation measures beyond the product information:* - Routine signal management - PSUR
Psychiatric Disorders- including depression, suicidality and anxiety	Routine risk communication: Provide in SmPC section **4.4 Special warnings and precautions for use** Psychiatric disorders Psychiatric disorders Depression, depression aggravated, anxiety, aggressive tendencies, mood alterations, psychotic symptoms and, very rarely, suicidal ideation, suicide attempts and suicide have been reported in patients treated with isotretinoin (see section 4.8). Particular care needs to be taken in patients with a history of depression and all patients should be monitored for signs of depression and referred for appropriate treatment if necessary. However, discontinuation of isotretinoin may be insufficient to alleviate symptoms and therefore further psychiatric or psychological evaluation may be necessary. Provide in SmPC section **4.8 Undesirable effects** *Rare (≥1/10,000 to <1/1,000):* Depression, depression aggravated, aggressive tendencies, anxiety, mood alterations. *Very rare (≤1/10,000):* Abnormal behaviour, psychotic disorder, suicidal ideation, suicide attempt, suicide Associated wording is included in the PIL. *Other routine risk minimisation measures beyond the product information:* - Routine signal management - PSUR
Severe increase in triglyceride levels,	Routine risk communication: Provide in SmPC section **4.4 Special warnings and precautions for use**

sometimes associated with acute pancreatitis	Lipid metabolism Serum lipids (fasting values) should be checked before treatment, 1 month after the start of treatment, and subsequently at 3 monthly intervals unless more frequent monitoring is clinically indicated. Elevated serum lipid values usually return to normal on reduction of the dose or discontinuation of treatment and may also respond to dietary measures. Isotretinoin has been associated with an increase in plasma triglyceride levels. Isotretinoin should be discontinued if hypertriglyceridaemia cannot be controlled at an acceptable level or if symptoms of pancreatitis occur (see section 4.8). Levels in excess of 800 mg/dL or 9 mmol/L are sometimes associated with acute pancreatitis, which may be fatal. Provide in SmPC section **4.8 Undesirable effects** *Very common* (≥1/10) Blood triglycerides increased, high density lipoprotein decreased *very rare (≤1/10,000)* Hepatitis Associated wording is included in the PIL. *Other routine risk minimisation measures beyond the product information:* - Routine signal management - PSUR
Severe allergic reactions	Routine risk communication: Provide in SmPC section **4.4 Special warnings and precautions for use** Allergic reactions Anaphylactic reactions have been rarely reported, in some cases after previous topical exposure to retinoids. Allergic cutaneous reactions are reported infrequently. Serious cases of allergic vasculitis, often with purpura (bruises and red patches) of the extremities and extracutaneous involvement have been reported. Severe allergic reactions necessitate interruption of therapy and careful monitoring. Provide in SmPC section **4.8 Undesirable effects** *Rare (≥1/10,000 to <1/1,000)* Allergic skin reaction, anaphylactic reactions, hypersensitivity Associated wording is included in the PIL. *Other routine risk minimisation measures beyond the product information:*

	- Routine signal management - PSUR
Eye disorders including corneal opacities, reduced night vision and keratitis	Routine risk communication: Provide in SmPC section **4.4 Special warnings and precautions for use** <u>Eye disorders</u> Dry eyes, corneal opacities, decreased night vision and keratitis usually resolve after discontinuation of therapy. Dry eyes can be helped by the application of a lubricating eye ointment or by the application of tear replacement therapy. Intolerance to contact lenses may occur which may necessitate the patient to wear glasses during treatment. Decreased night vision has also been reported and the onset in some patients was sudden (see section 4.7). Patients experiencing visual difficulties should be referred for an expert ophthalmological opinion. Withdrawal of isotretinoin may be necessary. Provide in SmPC section **4.7 Effects on ability to drive and use machines** A number of cases of decreased night vision have occurred during isotretinoin therapy and in rare instances have persisted after therapy (see sections 4.4 and 4.8). Because the onset in some patients was sudden, patients should be advised of this potential problem and warned to be cautious when driving or operating machines. Drowsiness, dizziness and visual disturbances have been reported very rarely. Patients should be warned that if they experience these effects, they should not drive, operate machinery or take part in any other activities where the symptoms could put either themselves or others at risk Provide in SmPC section **4.8 Undesirable effects** *Very common* (≥1/10) Blepharitis, conjunctivitis, dry eye, eye irritation *Very rare (<1/10,000)* Blurred vision, cataract, colour blindness (colour vision deficiencies), contact lens intolerance, corneal opacity, decreased night vision, keratitis, papilloedema (as sign of benign intracranial hypertension), photophobia, visual disturbances Associated wording is included in the PIL. *<u>Other routine risk minimisation measures beyond the product information:</u>* - Routine signal management

	- PSUR
Musculoskeletal and connective tissue disorders including bone changes and rhabdomyolysis	Routine risk communication: Provide in SmPC section **4.4 Special warnings and precautions for use** Musculo-skeletal and connective tissue disorders Myalgia, arthralgia and increased serum creatine phosphokinase values have been reported in patients receiving isotretinoin, particularly in those undertaking vigorous physical activity (see section 4.8). Bone changes including premature epiphyseal closure, hyperostosis, and calcification of tendons and ligaments have occurred after several years of administration at very high doses for treating disorders of keratinisation. The dose levels, duration of treatment and total cumulative dose in these patients generally far exceeded those recommended for the treatment of acne. Provide in SmPC section **4.8 Undesirable effects** *Very common* (≥1/10) Athralgia, myalgia, back pain (particularly adolescent patients) *Very rare (<1/10,000)* Arthritis, calcinosis (calcification of ligaments and tendons), epiphyses premature fusion, exostosis, (hyperostosis), reduced bone density, tendonitis Associated wording is included in the PIL. *Other routine risk minimisation measures beyond the product information:* - Routine signal management - PSUR
Severe skin reactions (including SJS and TEN)	Routine risk communication: Provide in SmPC section **4.4 Special warnings and precautions for use** Skin and subcutaneous tissue disorders Acute exacerbation of acne is occasionally seen during the initial period but this subsides with continued treatment, usually within 7-10 days, and usually does not require dose adjustment. Exposure to intense sunlight or to UV rays should be avoided. Where necessary a sunprotection product with a high protection factor of at least SPF 15 should be used. Aggressive chemical dermabrasion and cutaneous laser treatment should be avoided in patients on isotretinoin for a period of 5-6 months after the end of the treatment because of the risk of hypertrophic scarring in atypical areas and more rarely post

	inflammatory hyper or hypopigmentation in treated areas. Wax depilation should be avoided in patients on isotretinoin for at least a period of 6 months after treatment because of the risk of epidermal stripping. Concurrent administration of isotretinoin with topical keratolytic or exfoliative anti-acne agents should be avoided as local irritation may increase (see section 4.5). Patients should be advised to use a skin moisturising ointment or cream and a lip balm from the start of treatment as isotretinoin is likely to cause dryness of the skin and lips. There have been post-marketing reports of severe skin reactions (e.g. erythema multiforme (EM), Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN)) associated with isotretinoin use. As these events may be difficult to distinguish from other skin reactions that may occur (see section 4.8), patients should be advised of the signs and symptoms and monitored closely for severe skin reactions. If a severe skin reaction is suspected, isotretinoin treatment should be discontinued. Provide in SmPC section **4.5 Interaction with other medicinal products and other forms of interaction** Concurrent administration of isotretinoin with topical keratolytic or exfoliative anti-acne agents should be avoided as local irritation may increase (see section 4.4). Provide in SmPC section **4.8 Undesirable effects** *Very Common (≥1/10)* Cheilitis, Dermatitis, Dry skin, Localised exfoliation, Pruritus, Rash erythematous, Skin fragility (and risk of frictional trauma) *Rare (≥1/10 000 to <1/1 000)* Alopecia *Very Rare (*<1/10,000*)* Acne fulminans, Acne aggravated (acne flare), Erythema (facial), Exanthema, Hair disorders, Hirsutism, Nail dystrophy, Paronychia, Photosensitivity reaction, Pyogenic granuloma, Skin hyperpigmentation, Sweating increased *Not Known (cannot be estimated from the available data)* Erythema multiforme, Stevens-Johnson Syndrome, toxic epidermal necrolysis. Associated wording is included in the PIL.

	Other routine risk minimisation measures beyond the product information: - Routine signal management - PSUR
Benign intracranial hypertension	Routine risk communication: Provide in SmPC section **4.4 Special warnings and precautions for use** Benign intracranial hypertension Cases of benign intracranial hypertension have been reported, some of which involved concomitant use of tetracyclines (see sections 4.3 and 4.5). Signs and symptoms of benign intracranial hypertension include headache, nausea and vomiting, visual disturbances and papilloedema. Patients who develop benign intracranial hypertension should discontinue isotretinoin immediately. Provide in SmPC section **4.3 Interaction with other medicinal products and other forms of interaction** Cases of benign intracranial hypertension (pseudotumour cerebri) have been reported with concomitant use of isotretinoin and tetracyclines. Therefore, concomitant treatment with tetracyclines must be avoided (see section 4.3 and section 4.4). Provide in SmPC section **4.8 Undesirable effects** Very Rare *(*<1/10,000) Benign intracranial hypertension Convulsions, Drowsiness, Dizziness Associated wording is included in the PIL. *Other routine risk minimisation measures beyond the product information:* - Routine signal management - PSUR
Gastrointestinal disorders including inflammatory bowel disease	Routine risk communication: Provide in SmPC section **4.4 Special warnings and precautions for use** Gastrointestinal disorders Isotretinoin has been associated with inflammatory bowel disease (including regional ileitis) in patients without a prior history of intestinal disorders. Patients experiencing severe (haemorrhagic) diarrhoea should discontinue isotretinoin immediately. Provide in SmPC section **4.8 Undesirable effects** *Very Rare* (<1/10,000*)*

	Colitis, Ileitis, Dry throat, Gastrointestinal haemorrhage, haemorrhagic diarrhoea and inflammatory bowel disease, Nausea Associated wording is included in the PIL. *Other routine risk minimisation measures beyond the product information:* - Routine signal management - PSUR

V.2. Additional Risk Minimisation Measures

Teratogenicity and drug exposure during pregnancy

Healthcare Professional and Patient/Carer Guide

The term guide can refer to any descriptive material that educates Healthcare Professional and/or patients/caregivers about specific risks, and/or their early symptoms, and/or the best course of action to be taken when these appear beyond the recommendation contained in the Product Information. A guide may also aim to raise awareness about an on-going (imposed) registry/study, as well as about the general value of reporting adverse events. Terms such as 'brochure', 'leaflet' should be avoided and the term 'guide' should be used instead.

Pregnancy prevention programmes

A pregnancy prevention programme (PPP) is a set of interventions aiming to minimise pregnancy exposure during treatment with a medicinal product with known or potential teratogenic effects. The scope of such a programme is to ensure that female patients are not pregnant when starting therapy or do not become pregnant during the course and/or soon after stopping the therapy. It could also target male patients when use of a medicinal product by the biological father might have a negative effect on the pregnancy outcome. A PPP combines the use of educational tools with interventions to control appropriately access to the medicine. Therefore, the following elements should be considered individually and/or in combination in the development of a PPP.

• Educational tools targeting healthcare professionals and patients to inform on the teratogenic risk and required actions to minimise this risk e.g. guidance on the need to use more than one method of contraception and guidance on different types of contraceptives; information included for the patient on how long to avoid pregnancy after treatment is stopped; information for when the male partner is treated;

• Controlled access at prescribing or dispensing level to ensure that a pregnancy test is carried out and negative results are verified by the healthcare professional before prescription or dispensing of the medicinal product;

• Prescription limited to a maximum of 30 days' supply;

• Counselling in the event of inadvertent pregnancy and evaluation of the outcome of any accidental pregnancy.

Prescriber checklist

Used to facilitate patient selection when initiating therapy or repeat prescription is issued, as appropriate. The checklist should remind prescribers of e.g. a restricted indication, contraindications, warnings and precautions needed for the use of a medicinal product particularly relating to important safety concerns in the SmPC and to facilitate the need for examination of specific aspects of the patient's health before initiating treatment and/or during continuous monitoring as appropriate.

Objectives:

In order to assist prescribers, pharmacists and patients in avoiding foetal exposure to isotretinoin, the Stala Pharma provide educational materials to reinforce the warnings about the teratogenicity of isotretinoin, to provide advice on contraception before therapy is started and to provide guidance on the need for pregnancy testing.

Full patient information about the teratogenic risk and the strict pregnancy prevention measures as specified in the Pregnancy Prevention Programme should be given by the physician to all patients, both male and female.

Rationale for the additional risk minimisation activity:

The PPP is need to avoid foetal exposure to isotretinoin. Isotretinoin is a powerful human teratogen inducing a high frequency of severe and life-threatening birth defects.

Target audience and planned distribution path:

Educational materials for prescribers, pharmacists and patients are distributed via pharmaceutical representatives.

Educational materials for patients are distributed by prescribers.

To the prescriber:

- Physician Checklist/Acknowledgement Form for prescribing to Female Patients aiming to inform the doctors about the risks and prevention of teratogenicity.

To the pharmacist:

- Pharmacist checklist to isotretinoin dispensing aiming to inform the pharmacist about the risks and prevention of teratogenicity.

To the patients:

- Patient Information Sheet;

- Patient reminder card (including appointment table).

Plans to evaluate the effectiveness of the interventions and criteria for success:

How effectiveness of risk minimisation measures for the safety concern will be measured by monitoring the reporting rate of the reported cases.
Criteria for judging the success of the proposed risk minimisation measures:

- If no new safety data emerge providing evidence of increased frequency of Teratogenicity and drug exposure during pregnancy related ADRs.
- Planned dates for assessment periodically in the context of signal detection and in each PSUR/ PBRER.
- Results of effectiveness measurement Assessment in each update of RMP.
- Impact of risk minimisation: Labelling and packaging could be updated in accordance with new information which could lead to reinforcement of the current risk and direct healthcare professional communication (DHCP).

Neuropsychiatric effects

Healthcare Professional and Patient/Carer Guide

The term guide can refer to any descriptive material that educates Healthcare Professional and/or patients/caregivers about specific risks, and/or their early symptoms, and/or the best course of action to be taken when these appear beyond the recommendation contained in the Product Information. A guide may also aim to raise awareness about an on-going (imposed) registry/study, as well as about the general value of reporting adverse events. Terms such as ‘brochure’, ‘leaflet’ should be avoided and the term ‘guide’ should be used instead.

Objectives:

Particular care needs to be taken in patients with history of depression and all patients should be monitored for signs of depression or suicidal ideation.

Rationale for the additional risk minimisation activity:

The risk minimisation measures are being developed to ensure that healthcare professionals (HCPs) and patients are informed about the risks associated with oral retinoids before starting the treatment, and that adequate counselling regarding the risks is given.

Target audience and planned distribution path:

Educational materials for prescribers and patients are distributed via pharmaceutical representatives to prescribers and to the pharmacies they visit.

Educational materials for patients are distributed by prescribers.

To the prescriber

Doctor's guide for isotretinoin prescription aiming to inform the prescribers about the risks and prevention of psychiatric disorders.

To the pharmacist

Pharmacist guide to isotretinoin dispensing aiming to inform the pharmacist about the risks and prevention of psychiatric disorders.

A mention was added to reinforce the warning:

"in case your patient mentions to your symptoms that could be evocative of depressive disorders, do not hesitate to refer your patient to the prescriber"

To the patient

The guide aims to inform patients about the risks and prevention of psychiatric disorders.

Plans to evaluate the effectiveness of the interventions and criteria for success:

How effectiveness of risk minimisation measures for the safety concern will be measured by monitoring the reporting rate of the reported cases.

Criteria for judging the success of the proposed risk minimisation measures:

- If no new safety data emerge providing evidence of increased frequency of Teratogenicity and drug exposure during pregnancy related ADRs.
- Planned dates for assessment periodically in the context of signal detection and in each PSUR/ PBRER
- Results of effectiveness measurement Assessment in each update of RMP
- Impact of risk minimisation: Labelling and packaging could be updated in accordance with new information which could lead to reinforcement of the current risk and Dear healthcare professional communication (DHPC).

Severe lipid metabolism disorders with acute pancreatitis

Healthcare Professional and Patient/Carer Guide

The term guide can refer to any descriptive material that educates Healthcare Professional and/or patients/caregivers about specific risks, and/or their early symptoms, and/or the best course of action to be taken when these appear beyond the recommendation contained in the Product Information. A guide may also aim to raise awareness about an on-going (imposed) registry/study, as well as about the general value of reporting adverse events. Terms such as 'brochure', 'leaflet' should be avoided and the term 'guide' should be used instead.

Objectives:

The goal of this additional measure is to be aware of the risks associated with hypertriglyceridemia levels in excess which is sometimes associated with acute pancreatitis. Consequently, can be fatal.

Rationale for the additional risk minimisation activity:

The risk minimisation measures are being developed to ensure that healthcare professionals (HCPs) and patients are informed about the risks associated with oral retinoids and that adequate counselling regarding the risks is given.

Target audience and planned distribution path:

Educational materials for prescribers and patients are distributed via pharmaceutical representatives to prescribers and to the pharmacies they visit.
Educational materials for patients are distributed by prescribers.

To the prescriber, pharmacist and patient

Guides aim to inform about the risks of severe lipid metabolism disorders with acute pancreatitis and special biologic surveillance:
Serum lipids (fasting values) should be checked before treatment, 1 month after the start of treatment, and subsequently at 3 monthly intervals unless more frequent monitoring is clinically indicated.

Plans to evaluate the effectiveness of the interventions and criteria for success:

How effectiveness of risk minimisation measures for the safety concern will be measured by monitoring the reporting rate of the reported cases.

Criteria for judging the success of the proposed risk minimisation measures:

- If no new safety data emerge providing evidence of increased frequency of Teratogenicity and drug exposure during pregnancy related ADRs.
- Planned dates for assessment periodically in the context of signal detection and in each PSUR/ PBRER
- Results of effectiveness measurement Assessment in each update of RMP
- Impact of risk minimisation: Labelling and packaging could be updated in accordance with new information which could lead to reinforcement of the current risk and Dear healthcare professional communication (DHPC).

V.3 Summary of risk minimisation measures

Table 40 - Part V.3: Summary table of PhV activities and RMM by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Teratogenicity	Routine risk minimisation measures: SmPC **section 4.3** where is contraindicated the use of isotretinoin in women who are pregnant or breastfeeding. SmPC **section 4.4** where special warnings and precautions for use of isotretinoin is mentioned. SmPC **section 4.6** Associated wording is included in the PL section 2. **Labelling** also warning about the risks of teratogenicity. Additional risk minimisation measures: - Physician Checklist/ Acknowledgement Form for Prescribing to Female Patients - Pharmacist checklist - Patient Information Sheet - Patient Reminder Card	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: - AE follow-up form for adverse reaction - PSUR Additional pharmacovigilance activities: Post-Authorisation Safety Study (PASS) to evaluate de effectiveness of the implementation of these risk minimisation measures (RMMs).
Psychiatric Disorders- including	Routine risk minimisation measures:	Routine pharmacovigilance activities beyond adverse

Safety concern	Risk minimisation measures	Pharmacovigilance activities
depression, suicidality and anxiety	SmPC **section 4.4** Special warnings and precautions for use in Psychiatric disorders SmPC **section 4.8** Associated wording is included in the PL section 2 and 4. <u>Additional risk minimisation measures:</u> - Healthcare Professional Guide - Patient guide	reactions reporting and signal detection: - AE follow-up form for adverse reaction - PSUR Additional pharmacovigilance activities: Post-Authorisation Safety Study (PASS) to evaluate de effectiveness of the implementation of these risk minimisation measures (RMMs).
Severe increase in triglyceride levels, sometimes associated with acute pancreatitis	<u>Routine risk minimisation measures:</u> SmPC **section 4.4** where advice is given on monitoring the lipid levels. SmPC **section 4.8** Associated wording is included in the PL section 2 and 4. <u>Additional risk minimisation measures:</u> - Healthcare Professional Guide - Patient guide	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: - AE follow-up form for adverse reaction - PSUR Additional pharmacovigilance activities: Post-Authorisation Safety Study (PASS) to evaluate de effectiveness of the implementation of these risk minimisation measures (RMMs).
Severe skin reactions	<u>Routine risk minimisation measures:</u> SmPC **section 4.4** Special warnings and precautions for use. SmPC **section 4.8** Associated wording is included in the PL section 2 and 4.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: - AE follow-up form for adverse reaction - PSUR
Eye disorders including corneal	<u>Routine risk minimisation measures:</u>	Routine pharmacovigilance activities beyond adverse

Safety concern	Risk minimisation measures	Pharmacovigilance activities
opacities, reduced night vision and keratitis	SmPC **section 4.4** where advice is given relating to the eye discords. SmPC **section 4.7** where advice is given on the ability to drive and use machines. SmPC **section 4.8** Associated wording is included in the PL section 2 and 4.	reactions reporting and signal detection: - AE follow-up form for adverse reaction - PSUR
Musculoskeletal and connective tissue disorders including bone changes and rhabdomyolysis	Routine risk minimisation measures: SmPC **section 4.4** Special warnings and precautions for use. SmPC **section 4.8** Associated wording is included in the PIL PL section 2 and 4.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: - AE follow-up form for adverse reaction - PSUR
Severe skin reactions (including SJS and TEN)	Routine risk minimisation measures: SmPC **section 4.4** Special warnings and precautions for use. SmPC **section 4.5 and 4.8** Associated wording is included in the PL section 2 and 4.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: - AE follow-up form for adverse reaction - PSUR
Benign intracranial hypertension	Routine risk minimisation measures: SmPC **section 4.4** Special warnings and precautions for use. SmPC **section 4.5 and 4.8** Associated wording is included in the PL section 2 and 4.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: - AE follow-up form for adverse reaction - PSUR
Gastrointestinal disorders including inflammatory bowel disease	Routine risk minimisation measures: SmPC **section 4.4** Special warnings and precautions for use. SmPC **section 4.8**	Routine pharmacovigilance activities beyond adverse

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	Associated wording is included in the PL section 2 and 4.	reactions reporting and signal detection: - AE follow-up form for adverse reaction - PSUR

Part VI: Summary of the risk management plan

Summary of risk management plan for Isotretinoin generics (Isotretinoin)

This is a summary of the risk management plan (RMP) for isotretinoin generics. The RMP details important risks of isotretinoin generics, how these risks can be minimised, and how more information will be obtained about isotretinoin generics' risks and uncertainties (missing information).

Isotretinoin generics' summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how isotretinoin generics should be used.

I. The medicine and what it is used for

Isotretinoin generics is authorised for severe forms of acne (such as nodular and conglobate acne or acne at risk of permanent scarring) resistant to adequate courses of standard therapy with systemic antibacterial and topical therapy (see SmPC for the full indication). It contains isotretinoin as the active substance and it is given by oral use by soft capsules with 10 mg of isotretinoin.

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of Isotretinoin generics, together with measures to minimise such risks and the proposed study for learning more about Isotretinoin generics' risks, are outlined below.
Measures to minimise the risks identified for medicinal products can be:
Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
Important advice on the medicine's packaging;

The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;

The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.
Together, these measures constitute routine risk minimisation measures.

In the case of Isotretinoin generics, these measures are supplemented with additional risk minimisation measures mentioned under relevant important risks, below.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment - so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

II.A List of important risks and missing information

Important risks of Isotretinoin are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Isotretinoin generics. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine);

Table 41 – List of important risks and missing information

List of important risks and missing information	
Important identified risks	Teratogenicity Psychiatric Disorders- including depression, suicidality and anxiety Eye disorders including corneal opacities, reduced night vision and keratitis Musculoskeletal and connective tissue disorders including bone changes and rhabdomyolysis Severe skin reactions (including SJS and TEN) Benign intracranial hypertension

List of important risks and missing information	
	Severe increase in triglyceride levels, sometimes associated with acute pancreatitis Severe allergic reactions
Important potential risks	Gastrointestinal disorders including inflammatory bowel disease
Missing information	Not applicable

II.B Summary of important risks

Table 42 – Summary of important risks

Important identified risk	
Teratogenicity	
Risk minimisation measures	Routine risk minimisation measures - AE follow-up form for adverse reaction - PSUR Additional risk minimisation measures - Physician Checklist/Acknowledgement Form for Prescribing to Female Patients; - Pharmacist Checklist; - Patient Information Sheet; - Patient Alert Card (including appointment table).
Psychiatric Disorders- including depression, suicidality and anxiety	
Risk minimisation measures	Routine risk minimisation measures - AE follow-up form for adverse reaction - PSUR Additional risk minimisation measures - Healthcare Professional Guide - Patient guide

Important identified risk	
Severe increase in triglyceride levels, sometimes associated with acute pancreatitis	
Risk minimisation measures	Routine risk minimisation measures - AE follow-up form for adverse reaction - PSUR Additional risk minimisation measures - Healthcare Professional Guide - Patient guide

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of Isotretinoin Generics.

II.C.2 Other studies in post-authorisation development plan

There are no studies required for Isotretinoin Generics.

Part VII: Annexes

Annex 1 – EudraVigilance Interface

Annex 2 – Tabulated summary of planned, ongoing, and completed

Pharmacovigilance study programme

Table 43 - Annex II: Planned and on-going studies

Study	Summary of objectives	Safety concerns addressed	Protocol link Milestones
LE observational cohort safety study (study LE123) Category 3	To evaluate the effectiveness of the implementation of the risk minimisation measures	Teratogenicity Psychiatric Disorders- including depression, suicidality and anxiety Severe increase in triglyceride levels, sometimes associated with acute pancreatitis	Interim results: Not applicable Final study report submission: 9 September 2018

Annex 3 - Protocols for proposed, on-going and completed studies in the pharmacovigilance plan

The study above is not imposed and not required for this reason the protocol is not included.

Annex 4 - Specific adverse drug reaction follow-up forms

Table of contents

Follow-up forms

ADVERSE DRUG REACTION FOLLOW-UP FORM

File number: |__|__| - |__|__|__|__| - |__|__|__|__|

PATIENT IDENTIFICATION

Last name (First 3 letters) : |__|__|__| **Sex : F □ M □**

First name (First 2 letters) : |__|__|

SUSPECTED DRUG INVOLVED:

Trade Name: _____ Dosage: _____

Indication (specify the severity):_____

Date of onset of reaction: ___/___/___ Time to onset of reaction: ___/___/___

DESCRIPTION OF THE ADVERSE(S) REACTION(S)

_____

_____

_____

FOLLOW-UP **RESULTS OF ANY ADDITIONAL EXAMINATIONS ordered following the side effect** (Attach photocopies if possible)	
Signature_____	Date___/___/___
Signature_____	Date___/___/___

Signature_____	Date___/___/___
Signature_____	Date___/___/___

CLOSED CASE TO FOLLOW-UP

Case without further information to receive:		**Impossibility of following-up**	
Results with known final	☐	Non collaboration with the notifier	☐
Assessment made by the notifier	☐	Loss of contact with the notifier	☐
Knowledge of the important data required for the case assessment	☐	Loss of contact between the notifier and the patient	☐
Signature_____		Date___/___/___	

Annex 5 - Protocols for proposed and on-going studies in RMP part IV

This section is not applicable

Annex 6 - Details of proposed additional risk minimisation activities

Draft key messages of the additional risk minimisation measures

Physician educational material:

- The Summary of Product Characteristics
- **Guide for healthcare professionals**:
  - Relevant information of the safety concern(s) addressed by the aRMM (e.g. seriousness, severity, frequency, time to onset, reversibility of the AE as applicable);
  - Details of the population at higher risk for the safety concern addressed by the aRMM (e.g. contraindications, risk factors, increased risk by interactions with certain medicine);
  - Details on how to minimise the safety concern addressed by the aRMM through appropriate monitoring and management (e.g. what to do, what not do, and who is most likely to be impacted according to different scenarios, like when to limit or stop prescribing/ingestion, how to administer the medicine, when to increase/decrease the dosage according to laboratory measurements, signs and symptoms);
  - Key message to convey in patients counselling;
  - Instructions on how to handle possible adverse events.
- **Prescriber checklist**:
  - Lists of tests to be conducted for the initial screening of the patient;
  - Premedication, general health, and pregnancy and contraception checks immediately before/during/after treatment;
  - A specific reference to the fact that the patient has been informed and understands the potential teratogenic risks of foetal malformations and the measures to minimise them.

The patient information pack:

  - Patient information leaflet
- **Patient/carer guide**:

- A description of the potential teratogenic risks(s) associated with the use of Isotretinoin Generics namely: foetal malformations.
- A description of the correct use of Isotretinoin Generics and the potential risks associated with its use, namely: foetal malformations, psychiatric disorders – including depression, suicidality and anxiety and severe increase in triglyceride levels, sometimes associated with acute pancreatitis.
- Recommendations for the planning of the monitoring schedule

For pregnancy-related risks:

- Recommendation not to take Isotretinoin Generics in case of pregnancy
- For women of child bearing potential recommendation to use effective contraception methods
- Recommendation for regular pregnancy testing

Annex 7 - Other supporting data (including referenced material)

Isotretinoin Generics 10/0000/m1/eu/13-pi/13.1-pil/Portugal

Isotretinoin Generics 10/0000/m1/eu/13-pi/13.1-SmPC/Portugal

Isotretinoin Generics 10/0000/m1/eu/13-pi/13.1-Labelling/Portugal

Annex 8 – Summary of changes to the risk management plan over time

This is the first version of RMP of the medicinal product Isotretinoin Generics so the list of all significant changes to the Risk Management Plan over time is not applicable.

Risk Minimization Measures of Isotretinoin Generics

Retinoids are natural or synthetic vitamin A derivatives with pleiotropic effects that regulate cell differentiation, proliferation and apoptosis. First-generation retinoids include *retinol tretinoin* (all-*trans*-retinoic acid) *isotretinoin* (13-*cis*-retinoic acid) and *alitretinoin* (9-*cis*-retinoic acid). Second-generation retinoids also known as *aromatic retinoids* were created by alteration of the cyclic end group and include *acitretin*. Third-generation retinoids contain further modifications and are called *arotinoids.* Members of this generation include *tazarotene* and *bexarotene. Adapalene* a derivative of naphthoic acid with retinoid-like properties does not fit precisely into any of the three generations (42).
In general, dietary surveys have revealed that the average un-supplemented adult diet contains 7000 IU to 8000 IU/day of vitamin A (45).

The activity of retinoids is mediated by Nuclear Retinoid Receptors (RNR) belonging to the superfamily of receptors activated by steroids, thyroid hormone, vitamin D and peroxisome proliferation. Vitamin A is essential to human health and naturally occurring in the blood however concerns have arisen regarding its potential teratogenicity [42].

Whether excessive vitamin A intake possibly causes birth defects not only in animals but also in man represents a still unresolved public health concern (46). Due to the low incidence of possibly vitamin A-related malformations in man available data cannot convincingly define the upper safe limit of periconceptional vitamin A intake. One study suggests the possible teratogenic effects of high doses of vitamin A (40000 IU and more) when women were exposed to it during the organogenetic period (the first two months) (47). Human intervention studies are not feasible for ethical reasons.

Retinoid-containing medicinal products are available in oral and topical forms and are authorised both centrally and nationally. They are widely used to treat a variety of conditions mainly affecting the skin such as various forms of acne, severe chronic hand eczema unresponsive to corticosteroids, severe forms of psoriasis and keratinisation disorders (45).

Retinoids are recognised to be teratogenic at the recommended therapeutic dose of the oral formulations. The main known teratogenic effects are central nervous system, craniofacial, cardiovascular and thyme abnormalities (45).

Pregnancy is an absolute contraindication in the SmPCs for all oral retinoids in the EU. A referral in 2003 for isotretinoin led to introduction of the isotretinoin pregnancy prevention programme (PPP) in the EU. Since the introduction of the PPP for isotretinoin

similar programmes have been introduced for the other oral retinoids used to treat dermatological conditions. The effectiveness of these PPPs has been kept under close review and although a reduction in the number of pregnancies exposed to these retinoids has been observed cases of pregnancies exposed to retinoids continue to occur (42)

In 2016, the PRAC reviewed the effectiveness of the PPP for oral isotretinoin and noted post-marketing data and published studies raising concerns about how well the requirements of the PPP are followed in clinical practice. These data suggested that there were a large area that may impact on the effectiveness of the PPP including inconsistencies in information provided with regard to contraceptive measures and a lack of up-to-date information about the most effective contraceptive methods inadequate documentation of the required patient monitoring and potential differences in the pregnancy prevention programmes implemented across the generics. Consequently, the PRAC identified a need for a detailed assessment of compliance with the requirements of the PPP for isotretinoin (42).

In conclusion, PRAC considered there is a need to thoroughly review the routine risk minimisation (warnings in the SmPC and package leaflet) in place for the oral and topical retinoids to ensure the available data and the risks associated with the adverse teratogenic effects are accurately and consistently addressed within the product information where appropriate and justified by data. Furthermore, it is necessary to review any additional risk minimisation measures to ensure that these are optimal in terms of provision of information and delivery of effective risk management that is subject to appropriate monitoring (42).

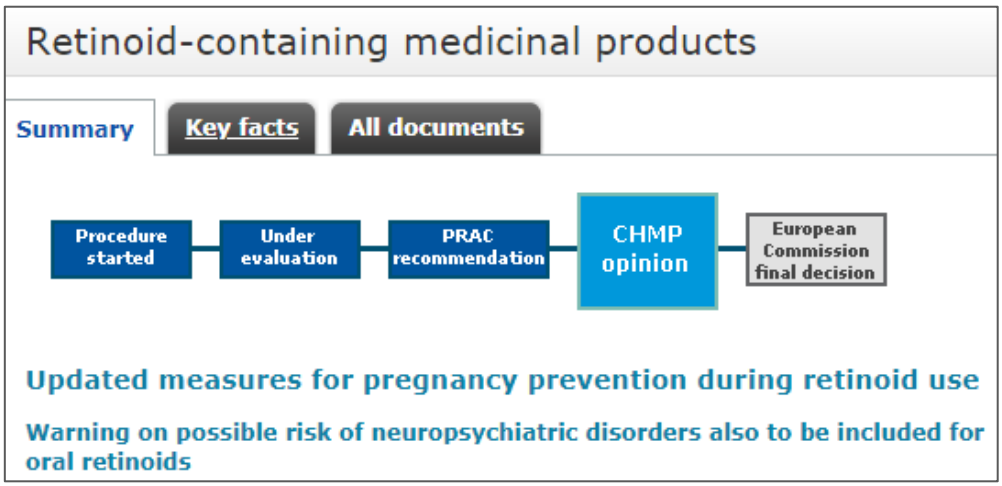
Therefore, on 7 July 2016 the UK Medicines and Healthcare Products Regulatory Agency (MHRA) triggered a referral under Article 31 of Directive 2001/83/EC and asked the PRAC to assess the impact of the above concerns on the benefit-risk balance of retinoid-containing medicinal products and issue a recommendation on whether the products should be maintained, varied, suspended or revoked (42).

As a result, in February 2018 the PRAC concluded its review of retinoid medicines and recommended updating the measures for pregnancy prevention and including a warning on the possible risk of neuropsychiatric disorders (such as depression, anxiety and mood changes) (42).
In March 2018 the European Medicines Agency has completed its review of retinoid medicines and confirmed that an update of actions for pregnancy prevention was

needed. In addition, a warning on the possibility that neuropsychiatric disorders (such as depression, anxiety and mood changes) may occur would be included in the prescribing information for oral retinoids (42).

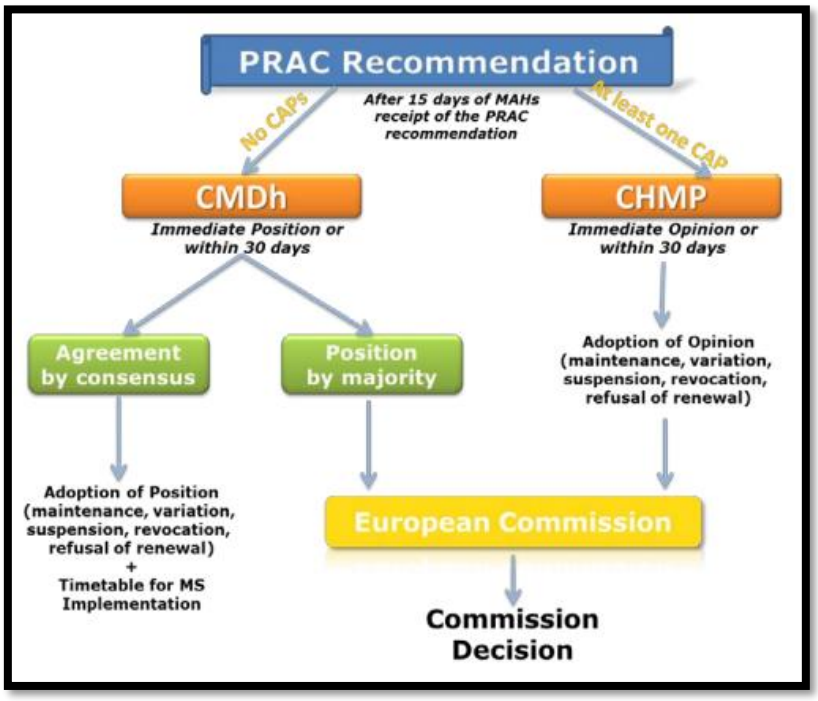
The steps of the referral process, taken from the website of EMA, for the retinoids and the final outcome are presented as following:

Figure 2: Steps during the referral process of isotretinoin



The CHMP opinion or the CMDh position by majority vote, was sent to the European Commission (EC), which took a final decision valid across the EU. (19,36)

Figure 3: The overall process including timelines for adoption of an opinion, position, or agreement.



Afterwards the EC initiated the decision-making process which led to the adoption of a binding decision addressed either to the MAHs or MSs, depending on whether the decision concerns centrally authorised products (CAPs) or nationally authorised products (including via the mutual recognition and decentralised procedures), respectively (19, 36)

Adequacy of existing PPP and proposals for any updates

It is the nature of the contraception (e.g. user independent forms such as implants or intrauterine devices) that is more likely to increase the effectiveness rather than the number of different forms used. With regards to pregnancy testing, the existing PPPs requires monthly pregnancy testing and the only exception is where the prescriber considers that there are compelling reasons to indicate that there is no risk of pregnancy and it seems important to retain this level of clinical discretion. It was noted there were several inconsistencies between the materials, not only between the different active substances but also between products with the same active substance (42, 43)

Regarding the key messages, although some differences could be detected among the different products, it seems that the problem may not be regarding the content of the materials as the majority cover information on the teratogenic risks, conditions of prescribing, conditions for dispensing, information about the contraceptive methods, information for doctor, pharmacist and patient, including guides and acknowledgement

form. However, the current approved materials are very extensive and the information among the same set of materials is repetitive and these could be made more concise and focused (42, 43).

It should also be highlighted that it would be important to reduce the number of different documents. Overly long and repetitive information does not enhance readability. Therefore, the materials should be made more concise and focused and this is true across all recipients – patients, physicians and pharmacists.

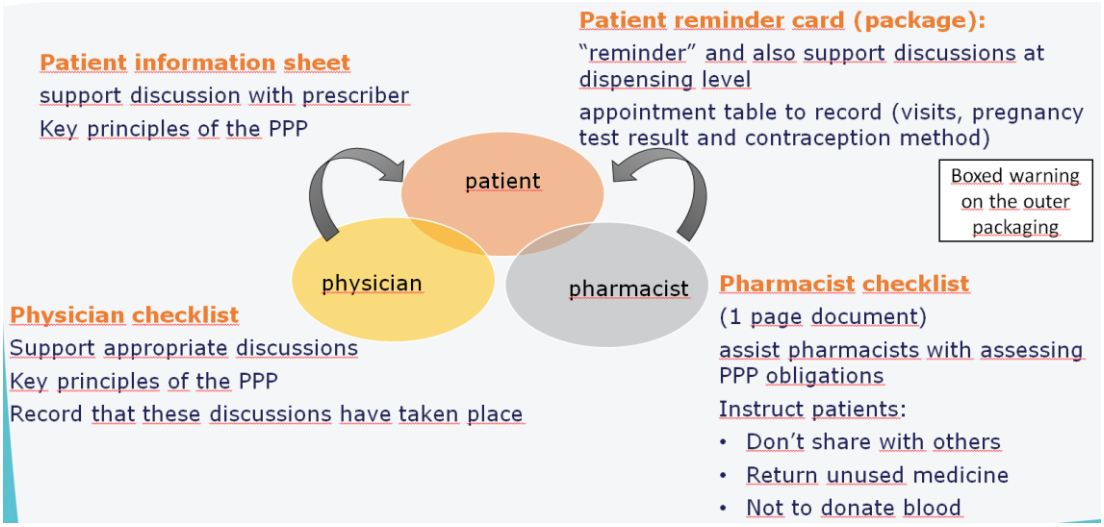
The PPP should be updated, in accordance with core elements and principles defined in advance. The aim was to harmonize and simplify information for patients and HCPs.

The following changes to the current educational materials are indicated in the following table:

Table 44 - changes to the current educational materials

	Previous educational materials	**Proposed educational materials**
Patient materials	Patient brochure	Patient information sheet
	Contraception advice brochure	
		Patient reminder card
Physician materials	Physician guide	
	Physician checklist Acknowledgement form	Physician checklist/acknowledgement form (merged document)
Pharmacist materials	Pharmacist brochure	Pharmacist checklist

Figure 4: Illustration of the proposed educational materials



Additionally, it is also considered necessary to improve not only the format and key messages of these materials, but also explore the possibility of electronic dissemination of these materials (e.g. website/URL, apps, SMS messaging), the feasibility of a patient reminder card inserted in outer packaging and also the possibility of using Quick Response code (QR code) on the outer packaging and package leaflet, among others (19, 43).

The following core elements and principles should be implemented in each material:
For all oral retinoids the key messages are:

a. Teratogenicity risk – what it means to the unborn fetus
b. Contraception – the 'risk period', and what measures need to be observed through this risk period
c. Pregnancy testing – why this is important, and why monthly prescriptions are required

For Isotretinoin Generics it is proposed to have now three educational materials, one for each of the patient, physician and pharmacist. Attached you can find the proposed educational materials.

Educational Materials for the patient, physician and pharmacist

1. Physician materials

Physician Checklist /Acknowledgement Form for Prescribing to Female Patients

The potential for pregnancy must be assessed for all female patients prescribed Isotretinoin Generics

A woman has a potential for pregnancy if one of the following applies:

Is a sexually mature woman who:

1) has not had a hysterectomy or bilateral oophorectomy

2) is not in a natural postmenopause for a minimum of 24 consecutive months (ie, menstruated at a certain point in the last 24 consecutive months).

Is the patient a woman of childbearing potential? Yes No

This checklist is to be completed by the Physician for all female patients prescribed Isotretinoin Generics and kept with patient notes to document compliance with the Isotretinoin Generics Pregnancy Prevention Programme. After completion a copy of this document should be given to the patient.

Isotretinoin Generics belongs to the retinoid class of drugs that cause severe birth defects. Foetal exposure to Isotretinoin Generics, even for short periods, presents a high risk of congenital malformations. Retinoids are strictly contraindicated in women of childbearing potential, unless all conditions in the Isotretinoin Generics Pregnancy Prevention Programme are fulfilled.

As the prescribing doctor, you must make sure that the risk of serious harm from drug exposed pregnancy is fully understood by all female patients before treating them with Isotretinoin Generics.

Before initiating Isotretinoin Generics therapy in a female patient, the following checklist must be completed and stored in the patient's notes. This checklist should also be used in all follow-up visits with women of childbearing potential.

Please use the patient information sheet to support your discussion with the patient.

Women with childbearing potential

Review the below statements, explain them to the patient and record confirmation of this and acknowledgment from the patient in this form. If the answer to any of these questions is **NO**, Isotretinoin Generics must not be prescribed.

Table 45 – Doctor's check list

	Doctor confirm: I have explained this to my patient [YES/NO]	Patient confirm: I have understood this [YES/NO]
Teratogenicity		
The patient understands that Isotretinoin Generics belongs to a class of drugs (retinoids) known to cause severe birth defects and that they must not get pregnant whilst taking it. Isotretinoin Generics also increases the risk of miscarriage when taken during pregnancy		
Contraception		
The patient understands that she must consistently and correctly use at least 1 and preferably 2 effective and complementary methods of birth control before and during treatment		
The patient understands that the risk persists even after the medication is stopped and that she must not get pregnant for 5 weeks after stopping treatment		
The patient has received advice on contraception which is appropriate for them and has committed to using it throughout the risk period		
The patient is aware of the risk of contraceptive failure		
Pregnancy Testing & Monthly Prescriptions		
The first prescription for Isotretinoin Generics can only be given after the patient has had one negative medically supervised pregnancy test. This is to make sure she is not already pregnant before starting treatment		
Patient Understands that only a 30 day supply can be given and the prescription must be used in 7 days.		

Patient understands the need for and agrees to pregnancy testing before, during and after treatment		
Patient understands the need to do a pregnancy test 5 weeks after stopping treatment because the drug stays in the body for 5 weeks after the last dose and can damage an unborn baby if pregnancy occurs.		
The contraceptive methods and pregnancy test results were recorded in the patient's appointment table (included in patient reminder card)		
The patient has received a copy of the educational package		
The patient knows to contact their doctor if they have unprotected sex, miss their period, become pregnant, or suspect that they have become pregnant during the risk period		
If pregnancy occurs, treatment must be stopped and the patient should be referred to an expert physician specialised or experienced in teratology for advice.		
Signature		
Date		

The pregnancy should be reported to the MAH Stala Pharma G though the address below, who will follow up with you to record the pregnancy outcome.

Contact details:

Stala Pharma G

QPPV: Patrícia de Lurdes Douteiro Rodrigues

Telephone: +351211122333

Telephone (24h): +351911122333

Fax: +351211122333

Address: Rua Alexandre Pinto, nº105, 3º esq, 2800-039 Lisbon, Portugal

Email: PhV@stalapharma.pt

Country: Portugal

2. Pharmacist Material

Pharmacist Checklist

Conditions for dispensing Isotretinoin Generics

Isotretinoin Generics belongs to the retinoid class of drugs that cause severe birth defects. Foetal exposure to Isotretinoin Generics, even for short periods, presents a high risk of congenital malformations and miscarriage.

Isotretinoin Generics is therefore strictly contraindicated in women of childbearing potential, unless all conditions in the Isotretinoin Generics Pregnancy Prevention Programme are fulfilled.

If you are aware that a pregnancy occurred in a woman treated with Isotretinoin Generics, treatment should be stopped immediately and the woman should be promptly referred to the prescribing doctor.

As pharmacist, you should only dispense Isotretinoin Generics after checking the following information:

Table 46 – Pharmacist's check list

For women of child-bearing potential:	
The prescription for Isotretinoin Generics is limited to a 30-day supply without refills (repeat prescriptions are not permitted)	
Prescriptions are dispensed within 7 days of the prescription date. (Prescriptions presented more than 7 days after the prescription date should be considered expired and the patient should be told to get a new prescription from their prescriber)	
Ideally, pregnancy testing, issuing a prescription and dispensing Isotretinoin Generics should occur on the same day	
For men:	
Prescriptions do not have a limit on the duration of treatment to be dispensed or restriction on the period the prescription is considered valid.	
All patients should be instructed:	
Never to give the Isotretinoin Generics to another person	
To return any unused capsules to their pharmacist at the end of treatment	
Not to donate blood during Isotretinoin Generics therapy and for one month after discontinuation due to the potential risk to the foetus of a pregnant transfusion recipient	

3. Patient materials

Patient Information sheet

Isotretinoin Generics belongs to a class of drugs (retinoids) known to seriously damage an unborn baby if used in pregnant women.

Treatment with Isotretinoin Generics during pregnancy is not allowed under any circumstances.

This patient information sheet contains important information about your treatment with Isotretinoin Generics and the risk of possible birth defects and miscarriage when taking this medicine.

Before taking Isotretinoin Generics, read this patient information sheet carefully to understand important facts about Isotretinoin Generics.

This guide complements but does not replace the instructions given to you by your doctor or pharmacist.

Further important information about Isotretinoin Generics, including how to take it, possible side effects and special warnings, are included in the patient information leaflet supplied in each package of Isotretinoin Generics. Please remember to read the package leaflet very carefully.

If you have any questions or concerns about taking Isotretinoin Generics after reading this guide, please ask your doctor or pharmacist.

You will also receive a patient reminder card to care with you at all time to remind you of what you need to be aware of and comply with when taking Isotretinoin Generics.

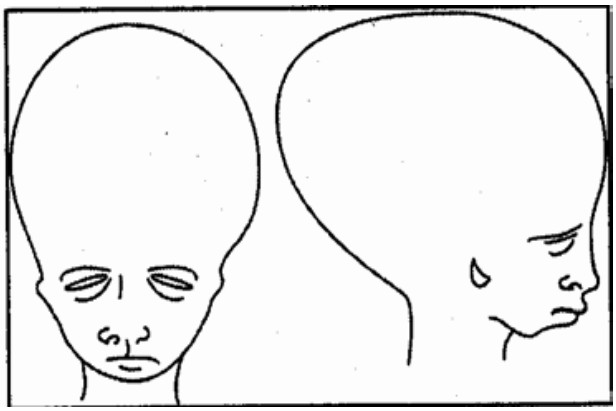
This medication has been prescribed to you only, do not share it with others and return any unused capsules back to the pharmacy.

Information about birth defects

Women of childbearing potential are not allowed to use Isotretinoin Generics, unless all instructions described in this guide are being followed.

This medicine is likely to seriously damage an unborn baby (i.e. is teratogenic).

This means that if you take Isotretinoin Generics during pregnancy, even for a short period of time, there is a very high risk that your baby will be born with birth defects.



This diagram represents the possible external malformations in the event of pregnancy during treatment with Isotretinoin Generics: no ear(s) or ears attached low down, large head and small chin, eye abnormalities, palate malformations. Internal malformations also frequently occur. These concern the heart, the thymus, the nervous system, and the parathyroid gland.

Before you take Isotretinoin Generics:

- **You must not take Isotretinoin Generics if you are pregnant.**
- You must use effective contraception at for at least one month before beginning treatment, during treatment, and for one month after Isotretinoin Generics treatment has stopped.
- As any contraceptive method can fail **it is strongly recommended that you use two forms of contraception at the same time**. However, this does not replace the discussion you need to have with your doctor. Your doctor will give you advice on the most effective contraception that is appropriate for you, taking into account your individual circumstances.
- **You must not become pregnant** while taking Isotretinoin Generics, or for 1 month after stopping treatment as there is an extremely high risk of severe birth defects.

Pregnancy testing and monthly prescriptions:

- You must have at least one negative medically supervised pregnancy test before treatment initiation. This is to make sure that you are not already pregnant on starting treatment with Isotretinoin Generics.
- Prescriptions of Isotretinoin Generics will only be for a maximum of 30 days. The reason for this is to ensure that **you visit your doctor every month** to ensure that you are following a suitable contraception method and to rule out a possible pregnancy.
- For further prescriptions, you must have a negative medically supervised pregnancy test every month.
- Your doctor will only provide a prescription for Isotretinoin Generics if there is a confirmed pregnancy test showing that you are not pregnant.
- You must agree to follow up visits every month and more pregnancy tests if you doctor asks you.
- You will also have a pregnancy test 5 weeks after stopping treatment.
- You will only be able to get your Isotretinoin Generics within 7 days from the date of the prescription. The pharmacy will not dispense your prescription beyond this seven-day deadline.

If there is any possibility you might be pregnant, <u>stop taking Isotretinoin Generics immediately</u> and contact your doctor.

During every monthly visit, your doctor will record the contraceptive methods and pregnancy test results in the appointment table included in your patient reminder card.

Please remember to bring the patient reminder card to every visit!

Patient reminder card (including appointment table)

Patient Reminder Card

Doctor's name:

Telephone:

Isotretinoin Generics belongs to a class of drugs (retinoids) known to seriously damage an unborn baby if used in pregnant women.

Treatment with Isotretinoin Generics during pregnancy is not allowed under any circumstances.

If there is any possibility you might be pregnant, stop taking Isotretinoin Generics immediately and contact your doctor.

Read the package leaflet and Patient information sheet carefully before you start treatment.

If you have any further questions or concerns about taking Isotretinoin Generics, talk to your doctor or pharmacist

What you have to do:

- **You must use at least one, but preferably two effective forms of contraception at least one month before beginning treatment, during and for 1 month after stopping treatment**
- **You must not become pregnant** while taking Isotretinoin Generics, or for 1 month after stopping treatment as there is a an extremely high risk of severe birth defects
- **You must attend monthly follow-up visits and have regular pregnancy testing:**

- Before treatment initiation you will have to have a pregnancy test, which must be negative.

- To make sure you are not pregnant during treatment, you must perform monthly pregnancy testing

- You will have to perform a pregnancy test 5 weeks after completion of treatment

This medication has been prescribed to you only, **do not share it with others and return any unused capsules back to the pharmacy**.

Appointment table

Please use this table to record the dates of your appointments with your doctor:

Doctor's name: **Telephone:**

Table 47 – Patient's Appointment table

Date of appointment	Contraception used	Pregnancy test result*	Doctor's Signature
		☐ **Positive** ☐ **Negative** **Date:**	
		☐ **Positive** ☐ **Negative** **Date:**	
		☐ **Positive** ☐ **Negative** **Date:**	
		☐ **Positive** ☐ **Negative** **Date:**	
		☐ **Positive** ☐ **Negative** **Date:**	
		☐ **Positive** ☐ **Negative** **Date:**	
		☐ **Positive** ☐ **Negative** **Date:**	

* If pregnancy test is positive, treatment must be stopped immediately and you must be urgently referred to a physician specialized or experienced in teratology for advice.

Have the last pregnancy test requested by your doctor done 5 weeks after stopping treatment.

4. Discussion/Conclusion

The pharmacovigilance activities have continuously evolved. Initially based mainly on the analysis of case reports, effective in detecting serious and rare ADRs, pharmacovigilance has evolved into a quality system - based scientific discipline and set of activities that include the whole spectrum of evidence relevant to monitoring medicines on the market.

The EU pharmacovigilance system embraces this broad scope and is founded on a proactive, risk proportionate and above all patient-centered approach to promoting and protecting public health. This public health-oriented system is characterized by responsiveness to new and emerging safety information, and continual effectiveness monitoring in an environment of transparency and openness. The system also strives for increased efficiency, by focusing on what works, streamlining processes and reducing duplication, with more efficiency efforts to be seen in the coming years.

The evolution of the EU pharmacovigilance system, especially after 2012, has had the achievement of better and faster decisions for medicine use as its main goal. Pivotal to this is the provision of up-to-date information and warnings to patients.

Pharmacovigilance departments are finding their roles have become increasingly strategic. Not only due to higher number of more complex regulatory requirements but also the involvement in some high-level business and inter-department activities within their own company. This complexity has led to an increase search of outsourcing of PhV-related services. For most companies, mainly bigger companies (with many associated affiliates), delegating part or total PhV activities will become the most cost-effective solution. However, for small or medium-sized companies the monitoring of these complex regulations become unsustainable, manely for generics enterprises.

Since the new pharmacovigilance regulations have come into force, any new MA application is to include a RMP. This enables the identification of the safety profile of a medicine and characterization of the risk induced based on the available data (identified risk, potential risk, etc.), to work out the measures to prevent or minimise the risk, and the measures necessary to assess the impact of any such minimisation.
A RMP must be adjusted to the particular product´s needs and to take into account the real-life setting, otherwise it may not be successful.

The RMP must be accompanied by the adequate PhV/RMMs to prevent or minimize the risks in order to promotes an optimal use of the product.

The PRAC is systematically consulted for any new medicine authorised by a centralised procedure or for any significant change in existing RMPs. The aim of the PRAC is in particular to ascertain the feasibility and the effectiveness of the RMPs.

The PRAC is a key component of the new regulation and community decisions in pharmacovigilance. We can see the work developed by the committee in the assessment of all aspects of the risk management of isotretinoin. In this case, despite the PPP program installed, the exposed pregnancies have continued to occur and the recommendations do not seem to have been applied by health care professionals and patients. Thus, the PRAC started a review of retinoid medicines in 2016 and in March of 2018 made a decision and elaborated recommendations, such as the RMM here presented. However, the implementation of aRMMs needs to be followed and assessed to ensure its effectiveness and if not successful they need to be reassessed.

In the same way, the formal inclusion of patients in spontaneous reports is part of the present trend to foster a more proactive pharmacovigilance system. Having more information about ADRs by including the medicines end-users can eventually allow for the identification of new risks in a given subgroup of patients. However, the spontaneous report system has weakness, of which the most important is under-reporting. The under-reporting delays the detection and identification of safety problems, making it more difficult for health authorities to act and preserve public health.

In the future, the EU PVh System must focus on enhancing further the involvement of patients and increasing the EU capacity for real-world evidence by harnessing the power of technology in using tools offered by healthy services or mobile services. The measurement of the effectiveness of risk minimisation measures must become more routinely embedded into pharmacovigilance activities.

To summarize, the PhV legislation and its complexity are leading to a high-level burden to ensure all the requirements are met and, as we saw by these practical examples, these are not always successful. Therefore, one may question the potential need to simplify the system in order to have more effective results.

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